BIOANALOGIC APPROACH TO IMPLANTS AND IMPLANTABLE MATERIALS

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MEDICEM is in the business of research and development of bioanalogic* medical devices in general, and functional bioanalogic implants in particular. Our “bioanalogic approach” comprises a selective application of various structural principles learned from the nature to synthetic implantable materials and to the implant design. We thus create an artificial functional analogy, rather than an exact copy, of the biological tissue, the structure or the organ that our device aims to replace, to repair or to improve.

We believe that in this way we can achieve the best possible, long-lasting and “natural” function without copying the tissues or organs directly as it is attempted by the tissue engineering approach that thus has to accept certain limitations of natural tissues such as lack of sterility, limited shelf-life, perhaps some ethical problems and inherent unpredictability of biological processes.

MEDICEM has learned bioanalogic approach to biomedical problems from its late mentor, Professor Otto Wichterle. This approach can be briefly stated in the following way:

“ORGANISM IS A VERY COMPLICATED SYSTEM COMPOSED FROM MANY ORGANS, BIOMOLECULES AND TISSUES. WE CANNOT POSSIBLY HOPE TO KNOW ALL THEIR POTENTIAL INTERACTIONS UNDER VARIOUS CIRCUMSTANCES AND/OR ANTICIPATE ALL POSSIBLE CONSEQUENCES. THEREFORE, IF WE REPLACE OR REPAIR SOME TISSUE USING AN ARTIFICIAL PART, IT IS SAFER TO CREATE AN ANALOGY OF THE LIVING PART IN AS MANY RESPECTS AS WE CAN, EVEN THOUGH WE MAY NOT BE CERTAIN ABOUT THE FUNCTION OR THE IMPORTANCE OF PARTICULAR FEATURES OR STRUCTURES”

Wichterle took this approach very long before emergence of tissue engineering (TE) which, of course, attempts to recreate the part in all its details, introducing thus many vulnerabilities inherent to living tissues. Contrary to the TE, bioanalogic approach utilizes also strong features of synthetic macromolecular compounds: long-term hydrolytic and enzymatic stability, sterilizability, processability into precise shapes, reproducible manufacturability, etc.

One can say that bioanalogic approach overarches the domains of purely biological approach (e.g. TE, regenerative medicine and transplants) and traditional biomedical engineering approach (applying engineering skills, materials and techniques to the development of medical devices) and utilizing both to the best advantage.

To get better understanding of the difference between the BioAnalogic (BA) and Biomedical Engineering (BE) approach, let us consider the case of ophthalmic lenses in general:

It all started with spectacles, the refractive device that is placed in a rather unnatural, unphysiological position pretty far in front of the cornea. Spectacles are clearly a BE rather than BA device since there is no analogy for them in biology. And sure enough, this BE device required rigid, impermeable materials with high refractive index (such as mineral or organic glass - PMMA) that were well established in non-medical optical applications. This provided spectacle lenses with high optical resolution, environmental stability, mechanical strength, and relatively thin and light-weight design.

Then ophthalmic lenses moved to a “more convenient” position contacting the eye surface, and the first contact lens was born. The first contact lenses were made from hard, non-permeable materials, precisely machined and polished, as their inventors learned from spectacle lenses. After all, the BE approach considered the contact lens as a modified spectacle lens that was moved to optically more advantageous, and cosmetically perhaps more appealing, position. Needless to say that the contact of the hard, impermeable material with the living tissues of cornea, conjunctiva, eyelid, etc. was not particularly comfortable or very physiologic and created numerous problems. One of the problems was the lack of adhesion of the hard lens to the eye surface - some of us will remember pictures of whole basketball teams on their knees looking on the court for a lost contact lens in the late 1960’.

Then came Wichterle with his BA idea of the hydrogel contact lens. He considered the contact lens not as a spectacle lens shrunk to fit under the eyelid, but as an extension of the

* In our usage, the term “bioanalogic” is a subset of the broader and far more familiar term “biomimetic”. While biomimetic approach may relate also to, inter alia, pharmaceutical compounds, architecture, military equipment, electronic circuits or sonar signal processing algorithms, we apply the term bioanalogic strictly to design of medical implants and synthetic implantable materials
cornea with a different surface curvature. The material for such a contact lens should then have properties analogic to those of the cornea - clear, flexible and highly hydrated material with relatively low refractive index that is well wetted by tears and permeable for water, oxygen, nutrients and metabolites.

Therefore, the material for the BA contact lens had to be also bioanalogic to mimic the essential properties of human cornea. It was obviously difficult to copy the cellular structure of a living tissue, such as cornea, by some synthetic means. It can be noted, however, that many properties of cellular tissue - water content, modulus of elasticity, refractive index, heat capacity, conductivity, permeability for aqueous solutes, etc. are derived from osmotic pressure of water-soluble macromolecules entrapped within the cells behind the semipermeable cellular membranes.

Rather than replicating such a cellular structure with caged macromolecules, Wichterle created a functional analogy of such structure by tying the water-soluble macromolecules to each other by covalent links. The resulting three-dimensional network controlled and limited the thermodynamically driven dilution of the macromolecules analogically to the cell membranes in the tissues preventing unlimited dilution of the water-soluble biomolecules in cells. Bioanalogic hydrogels based on sparingly cross-linked Poly(2-HEMA)¹ have become the first functional analogues of living tissue, and were used as material for the first bioanalogic corneal supplement that effectively changed refraction on the eye surface - hydrogel contact lens.

From combination of these two BA approaches a hydrogel contact lens was born that is now basis for the current multi-billion-dollar industry*. Concurrently with development of the first hydrogel contact lens, Wichterle noted certain similarity of the newly invented hydrogels with the material forming the natural crystalline lens. He created a bioanalogic implant from the PHEMA hydrogel in the shape and size similar to the natural crystalline lens. Prototypes of the first BAIOL were implanted in late 1950's¹². This idea of the BA IOL came, however well before its time. The IOL surgery has just in its infancy and it was dominated by the BE approach - the first IOLs were hard, carefully engineered PMMA lenses designed to resemble more spectacles than the natural IOL. Besides, the first hydrogels were not ready yet for the demanding role of the long-term ophthalmic implant, and several more decades of research and development were needed to create truly bioanalogic hydrogels and real bioanalogy of the natural crystalline lens.

Hydrogel development took three main avenues that contributed to the final success of bioanalogic implantable materials:

1) Improvements in network architecture that allow enhanced mechanical properties, increased hydration, better control over diffusive and hydraulic permeability characteristics, more predictable dimension changes etc. Substantial improvement came from partial or full replacement of covalent crosslinks by selected physical interactions - another BA feature since natural structures are mostly defined by physical bonding.

2) Fixed electric charge density is one of strong determinants of the organism’s response to an implant and to its interaction with proteins and cells. Hydrogels with balanced charge, and particularly with negative net charge are in this effect analogous to biological structures that do not elicit a foreign body reaction, such as hyaluronic acid-based intracellular matrices, fetal sack, amniotic membrane or glycocalyx of certain pathogenic bacteria.

3) Super-hydration of the implant surface helps to optimize its interaction with the tissue while achieving desirable bulk properties such as mechanical strength and modulus of elasticity and high refractive index that are difficult to combine with high water content and high density of fixed negative charge.

Combination of these approaches helped to beat the particularly vexing problem of the initial hydrogels, i.e. often unpredictable consequence of the healing process resulting sometimes in formation of mineral deposits and calcification of hydrogel implants. These effects posed problems in all types of implants (e.g., tissue augmentation, reconstruction of ducts and tendon liners), but they were particularly damaging to ophthalmic implants attempting to replace structures such as natural crystalline lens, vitreous body or cornea. Gradually, it was recognized that the calcification is closely related to interactions among hydrogel, cells and proteins from the body liquids. Based on these insights, the necessary know-how has been developed to formulate calcification-resistant hydrogels.

By-product of this research was better understanding of interactions between cells

* Wichterle contributed another BA idea to the development of hydrogel ophthalmic lenses: recognizing technical difficulties of precision molding of hydrogel lenses in closed solid molds, he noted that a liquid meniscus of e.g. a dew drop can form a lens; and in addition, he learned to control the meniscus shape by surface tension and by centrifugal forces. If the meniscus of the properly shaped monomer drop is solidified by e.g. polymerization, a hydrogel lens can be created in one single step without any mechanical operations. All original hydrogel contact and intraocular lenses were manufactured by this so called meniscus casting, and MEDICEM uses this manufacturing method today.
and hydrogel surface. These interactions can be now controlled to the extent that one part of the surface may be inert and cell-repulsing while the other part of the surface attracts cells to adhere, spread and proliferate.

The portfolio of bioanalogic hydrogels and related technologies enables MEDICEM to design bioanalogic implants that cannot be developed by using off-the-shelf polymers.

The prime example of this approach is WIOL-CF bioanalogic lens (Fig. 1) that utilizes a combination of proprietary features:

1) Bioanalogic WIGEL hydrogel that was developed and long-term tested specifically for intraocular applications,
2) Bioanalogic WIOL-CF shape of the lens aiming to fit into the space vacated by the natural lens and enable its accommodation,
3) Bioanalogic optical design utilizing polyfocal optics with the same refractive index as the natural crystalline lens,
4) Implantation in partly dehydrated state enabling lens injection through a smaller incision and its gradual growth in situ until it achieves its functional shape, size and optical properties, and
5) Spin-casting manufacturing method using solidification of a precisely formed liquid drop that avoids any mechanical operation - also inspired by nature.

The result is the implantable, presbyopia-correcting intraocular lens (WIOL-CF) that resembles natural crystalline lens more than spectacles and offers substantially differentiated clinical profile compared to e.g. multifocal IOLs that are examples of IOLs developed under the BE approach:

<table>
<thead>
<tr>
<th>BA Design WIOL-CF</th>
<th>BE Design multifocal IOLs</th>
<th>Benefit WIOL-CF</th>
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<tbody>
<tr>
<td>Bioanalogic hydrogel</td>
<td>Hydrophilic or hydrophobic acrylate</td>
<td>Negative charge of the material prevents protein/cell adsorption, ensures long-term stability of function, low PCO; softness of the material enables accommodation; refractive index similar to natural crystalline lens minimizes potential for disturbing optical phenomena</td>
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<tr>
<td>Full-optics (9 mm)</td>
<td>Small size optics (5-6 mm)</td>
<td>No edge-derived halo/glare, no loss of light, good peripheral and night vision, good posterior segment diagnostics</td>
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<tr>
<td>Smooth, continuous polyfocal optics</td>
<td>Refractive or diffractive zones optics</td>
<td>Continuous focus for all distances (i.e. not only in pre-defined distances), no loss of light, excellent mesopic contrast sensitivity above young population norm, stability of vision across changing light conditions, no zones-derived glares/halos (glares/halos at the level of monofocal IOLs)</td>
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In conclusion, we are persuaded that exclusive properties of bioanalogic hydrogels enable application of substantially different approaches and solutions compared to BE technologies in a wide number of ophthalmic surgery applications. We understand WIOL-CF as the first proof of this concept, that was taken to the stage of a certified medical device product (CE mark) and that confirms feasibility and utility of the BA approach. We are encouraged and committed to advance our bioanalogic hydrogel based portfolio in multiple applications across ophthalmic surgery, e.g. in bioanalogic IOLs with femtosecond laser adjustable optics, surgery-free transcorneal glaucoma valves maintaining IOP in pre-defined range, fixation-free anterior chamber lenses for refractive surgery, corneal/vitreous body prostheses or inlays, etc.