Nick Lane

Beyond the IOL

Nick Lane, PhD

IMPLANTING IOLs has become a way of life for many cataract surgeons – a routine operation that has dramatically improved the quality of life for millions of patients worldwide. But how close is the next step – a world beyond the IOL – where cataracts are dissolved, or the lens replaced with a new one grown from stem cells?

Back in December 2003 the British newspaper *The Daily Mail* ran a story that Russian scientists had developed an eye drop – N-acetyl-carnosine, or NAC – that dissolved cataracts in a matter of weeks. Not surprisingly, it made quite a splash, including a feature on daytime TV. If nothing else, it goes to show the appetite among the public for a quick fix not involving cataract surgery.

By May 2007, however, even a major website recommending NAC had put up a notice admitting that, in its experience, NAC didn't really work, and they'd stopped selling it. So is it all wishful thinking, or is there life beyond the IOL?

Dissolving – the evidence

Curiously enough, despite reassuring cataract surgeons that they shouldn't panic – yet – in April this year Randall J Olson, MD, of the Moran Eye Centre, University of Utah, presented evidence at the ASCRS in San Diego that another formulation, this time of the heavy-metal chelator EDTA, had the power to dissolve cataracts.

Previously hampered by its poor absorption across cell membranes, the permeability of EDTA was enhanced by methylsulfonylmethane (MSM) in these studies, enabling therapeutic concentrations to penetrate into the lens after topical application.

"We don't know exactly how it works," Dr Olson admitted to *EuroTimes*, "but the early case studies and anecdotal evidence were really striking; frankly, I'd seen nothing like it."

Nonetheless, Dr Olson was sceptical of generalising from individual cases, and insisted on designing some rigorous double-blind trials, culminating in a recently completed FDA phase II trial, which evaluated the effects of permeabilised EDTA on early nuclear cataracts.

We won't find out about the detailed results for a while yet, but they must be good, as Dr Olson is optimistic and told *EuroTimes* that he expects an FDA Phase III trial to begin within the year.

The topical treatment appears to 'clear' multilamellar bodies, which are found some 10 times more frequently in cataracts than in normal lenses, where they seem to promote light scatter and decreased visual function. Dissolving these multilamellar bodies, Olson says, can potentially reverse cataract formation, and also affect other conditions in which calcification plays a role, such as band keratopathy and asteroid hyalosis.

Remarkably, Dr Olson told *EuroTimes*, EDTA even shows signs of lowering IOP, perhaps through an action on the trabecular meshwork.

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"The removal of transition metals like iron and copper presumably lowers oxidative stress, but there must be more to it than that," said Dr Olson. "If EDTA functioned only as an antioxidant, I'd expect it to block cataract progression, but not reverse cataractogenesis, which is what we are actually seeing at least in some cases. It's possible that in suppressing oxidative stress we promote normal physiological repair mechanisms, reversing the injury."

On the other hand, Dr Olson noted that their data indicate an effect only on early nuclear cataracts so far, and EDTA seems to have little effect on cortical cataracts. This is a little surprising, as Dr Joseph Costello and his colleagues at the University of North Carolina, Chapel Hill reported 15 years ago that multilamellar bodies, and other light-scattering centres such as globules and vacuoles, occur far more frequently in the periphery of mature cataracts than in the nuclear core.

At that time, Dr Costello concluded that, "Subtle structural changes, especially small fluctuations in protein density between adjacent cells and alterations of the membranes and the extracellular space, probably contribute significantly to the central opacities in human nuclear cataracts."

It's noteworthy that few if any careful electron microscope studies have examined the distribution of multilamellar bodies in normal lenses and cataracts since then. So it might be that EDTA has more subtle effects on protein density and membrane structures in the nuclear core, not yet examined, and that the dissolution of multilamellar bodies does not influence the pathogenesis of cataract formation much.

After decades of equivocal if occasionally suggestive evidence that dietary antioxidants can hinder cataract formation, the time is ripe for some more serious clinical trials of topical formulations that could lower oxidative stress, perhaps promoting normal physiological repair mechanisms.

The FDA phase III trials will tell whether a permeabilised formulation of EDTA goes the same way as NAC, or offers genuine benefits. But the moral may not be the fortunes of any one particular therapy – there is a change in the wind, and the licence for dissolving cataracts isn't going to belong exclusively to the snake-oil sellers for much longer.

Silicone implants

Cortical cataract and posterior capsule opacification still raise knotty problems of their own. Posterior capsule opacification, in particular, has dogged the tracks of another technology that might be seen as 'beyond the IOL': capsular bag refilling with a silicone gel to provide an accommodating synthetic replacement for the crystalline lens.

Okihiro Nishi MD, of the Nishi Eye Hospital, Osaka, Japan, says he has solved the two problems that have bedevilled his work, and that of others, for the last decade – leakage from the capsulorhexis site, and – especially – posterior capsule opacification. Dr Nishi's team are planning to begin tests on primates this autumn, after successfully completing studies on rabbits (which are not capable of true accommodation).

Ironically, for a method that purports to be 'beyond the IOL', Dr Nishi's latest procedure involves implanting two IOLs, and filling the capsular bag between them with silicone gel. However, the new method is very consistent and reproducible, he told *EuroTimes*. "It can be performed by all cataract surgeons with a minimum of training."

Despite the many advantages of silicone as an implant material – it has a good refractive index, it's easy to inject and handle generally, and it's biocompatible – one big disadvantage is that it can take two or three hours to polymerise, during which time leakage from the anterior capsulorhexis is likely to be a problem.

Early solutions to this problem – inserting a silicone plug, for example – turned out to be technically demanding and poorly reproducible. Dr Nishi's recent solution is simply to place a foldable anterior IOL through the 3-4mm anterior capsulorhexis, and then inject the silicone (with the same refractive index) through the IOL, which then self-seals. It's simple and works very well, he told *EuroTimes*.

Blocking posterior capsule opacification proved to be an equally difficult hurdle to surmount, and Dr Nishi ultimately succeeded only through the use of a second IOL with sharp, square edges, implanted snugly onto the surface of the posterior capsule. An alternative approach that works equally well is a posterior capsulorhexis, sealed with a foldable IOL. Dr Nishi noted that both techniques were simple and reproducible to perform.

How effective this latest technique is in terms of accommodative amplitude, only time will tell. Early studies with silicone lenses on primates suggested that the degree of accommodation attainable was generally less than 3D – a clinically significant attainment, probably better than most accommodating IOLs (certainly after a couple of years), but still well below the 20 D range of natural accommodation.

But to increase accommodative power significantly beyond 4D, other procedures – such as dissolving the cataract or regenerating a clear crystalline lens – may ultimately hold more promise.

Grow your own lens

Dr Nishi concluded from his early primate studies that one factor missing from silicone implants was the accommodative power provided by intracapsular accommodation, which is to say the active participation of the lens fibre cells themselves.

In successfully blocking posterior capsule opacification, Dr Nishi, and indeed the entire research field, is surrendering any possibility of restoring full accommodation, as the natural re-growth of the lens is deliberately blocked.

The possibility of lens re-growth is by no means restricted only to newts and other amphibians and fish – mammals, including humans, have been known for a century or more to re-grow lens tissue after lens or cataract removal, so long as the capsule is intact. Only rarely, however, is a clear lens regenerated; more frequently, the new lens fibre cells are chaotically organised and opaque.

But from this point of view, posterior capsule opacification is not an outcome that ought to be avoided at all costs, but rather a dysfunctional attempt to re-grow a lens, one that could perhaps be fostered and improved upon. That, at least, is the unusual viewpoint of Dr Arlene Gwon MD, at the University of California, Irvine, and

Advanced Medical Optics, Inc, Santa Ana, California.

Dr Gwon confided to *EuroTimes* that she sometimes felt as if she was in a minority of one in viewing posterior capsule opacification as an improvable but inherently positive regenerate, rather than purely as an optical hindrance to be eradicated entirely if at all possible.

Even when the posterior capsule surface is cleaned very carefully after phacoemulsification, new fibre cells re-grow from the capsular epithelium into the capsular bag. According to Dr Gwon, this growth is chemotropic, attracted by cytokines and growth factors secreted by the anterior capsular epithelium.

Placing an IOL between the posterior and anterior surface distorts this signal, and leads to a confused growth of fibre cells in the posterior capsule – hence posterior capsular opacification. In contrast, the migration of epithelial cells along the anterior surface of the IOL leads to the re-growth of a clear lens in the anterior compartment of the capsular bag, where the signal is not distorted.

For the last two decades, Dr Gwon has been experimenting with various methods of encouraging the re-growth of clear lens fibre cells across the capsular bag. Inflating the bag after phacoemulsification with air or any other material to keep the capsule taut and to prevent the anterior and posterior capsule walls from sealing is the first critical point. If the capsular bag is inflated the regenerate lens will at least be lenticular in shape, even if it is opaque.

Beyond that, Dr Gwon's research has focused on providing a suitable scaffold to entrain fibre-cell growth, encouraging the parallel growth characteristic of the clear lens. Her most effective results have been obtained using hyaluronic acid – a polymer found in many connective tissues, which has been used to stimulate the re-growth of tissues in a variety of tissue-engineering settings.

Using a scaffold of hyaluronic acid, Dr Gwon has successfully re-grown a clear lens in rabbits, at least in a couple of instances. At present, the successful re-growth of a clear lens stands as proof of concept – proof that lens clarity is an attainable goal, given a more systematic understanding of the growth factors involved.

The penalty for failure can be serious, however – there are reported instances of a new lens growing straight through the anterior capsule as a stalk. Simply injecting stem cells into the capsular bag, Dr Gwon cautions, is unlikely to be successful.

Dr Gwon is the first to admit that there are plenty more hurdles to overcome. Lens growth is slower in humans than rabbits, for example, and in older people compared with younger people. It's slower, too, after cataract removal than after the removal of a clear lens. There are also a few technical difficulties that Dr Gwon has only recently solved; removing the hyaluronic acid scaffold after a few weeks using hyaluronase, for example, proved technically demanding.

Progress is slow, with few ophthalmologists pursuing research into lens re-growth, which is odd given the widespread interest in stem cell research. Here is a research field unburdened by ethical dilemmas, as it seems quite probable that the lens can regenerate without recourse to embryonic or any other type of stem cell other than those already in situ; yet there is little interest.

When should cataract surgeons panic?

So when will the world beyond the IOL put cataract surgeons out of a job? There are promising signs that powerful topical applications might block cataractogenesis, and reverse some aspects, dissolving existing cataracts. But ophthalmologists will rightly be circumspect at least until convincing phase III trial data have been published. This may be years away, and applicable to only a few types of cataract.

Lens refilling technologies look close to clinical realisation, and are likely to be a small improvement over multifocal or accommodating IOLs, especially when judged with a few years' follow-up. But this technology is not in any meaningful sense 'beyond the IOL', as capsular bag refilling will still require an accomplished cataract surgeon to implant twice as many IOLs.

And what of lens re-growth? At present rates of progress, Dr Gwon thinks it will be at least a decade before lens re-growth is a clinical reality. But in the end, this approach holds far more promise of a panacea for the majority of patients. Perhaps it is time that more cataract surgeons began thinking of lens re-growth as an attainable clinical goal. And it may even be an interesting new job somewhere down the line. Don't panic!