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In decade ahead, biotech may find its way into retinal treatment

Over the last 10 years, European ophthalmologists have heard much about the potential of biotechnology in treating eye disease. In the next 10 years, ophthalmologists may finally see some clinical impact from the laboratory.

Of course, any attempt to gaze into a crystal ball and identify areas of ophthalmic research that affect clinical practice 10 years from now must be a cautious exercise. However, even as subjective and cautious as such an exercise might be, three specific areas in the field of retinal disorders seem worthy of mention: gene identification, the prospect of corrective gene medicine and the landscape for new drug development.

The identification of particular genes involved in the pathogenesis of certain retinal disorders has quite literally exploded in recent times. Thanks to a number of critical technological advances, the research community presently sits astride – or under – a vast amount of data. With these advances comes the prospect of developing diagnostic tools for the pre-symptomatic identification of specific disorders in at risk populations.

The Human Genome Project has been a major engine of these advances, heralded with much pomp and ceremony in the summer of 2000 by no less than President Bill Clinton and Prime Minister Tony Blair when they jointly announced upon publication of the first draft of the human genome:

“With this profound new knowledge humankind is on the verge of gaining immense new power to heal. Genome science will have a real impact on all our lives, and even more on the lives of our children. It will revolutionise the diagnosis, prevention and treatment of most if not all, human disease”.

Genetics of AMD

Tangible evidence of such venerable goals was observed this year with a major advance in elucidating some of the genetic components behind age related macular degeneration (AMD). Studies, published in the journal *Science* provided conclusive evidence that a gene known as “complement factor H” (CFH), may be involved in AMD. The results of that study provided not only a highly promising drug target for the pharmaceutical industry, but also provided the basis for a new DNA assay for clinicians to identify asymptomatic patients who may be at risk of developing AMD.

Although several prior studies had implicated the role of a number of genes in AMD, the genes in those studies were linked to only a small minority of AMD cases. In contrast, the complement factor H gene could “likely explain” about 43% of cases of AMD in older adults, according to Dr Jonathan Haines, one of the researchers in the landmark study.

In a commentary on the AMD gene discoveries, Stephen Daiger MD, of the Human Genetics Centre of the University of Texas Health Sciences Centre, noted that the human genome project had contributed significantly to the recent breakthrough. “The human genome project is much more than the genetic map of our species. It is also a powerful set of integrated tools for solving problems in medicine and biology,” Dr. Daiger pointed out.

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“Application of these tools to a common cause of human blindness, age-related macular degeneration, implicates a common variant in the gene encoding complement factor H as a major contributor to the risk of developing the disease,” Dr. Daiger added. Echoing the statement of President Clinton and Prime Minister Blair, Dr. Daiger concluded that, “the new findings raise hopes for better diagnosis and treatment of macular degeneration and further validate the importance of the Human Genome Project.”

Dr. Daiger is as well placed as any to make such a judgement given his stewardship of a highly regarded open access database maintained at www.sph.uth.tmc.edu/Retnet. Over the past few years, the so-called “RetNet” database has published such information as tables of genes and loci linked to retinitis pigmentosa, macular degeneration, and Usher syndrome. Consider a summary of what RetNet says:

Between January of 1980 and January of 2004, researchers have mapped more than 150 gene loci and identified more than 100 genes. Armed with such valuable resources, the medical and research community can now consider how best to leverage value from such data not only to diagnose disease but also to design various strategies aimed at correcting these conditions at the genetic level.

Impact on clinical medicine remains small

A note of caution however is required. For the most part, the impact of genetics on the practice of clinical ophthalmology has been relatively minute. It is probably fair to say that research has provided more information concerning ocular diseases in the last 10 years than it has in the previous 100 years. However, the translation of data into knowledge and from knowledge into valuable tools and medicines has and will likely always lag behind. This is frustrating for the researchers, for the clinicians, and -- most of all -- for the patients. The next 10, 20 and 30 years will need to focus in on cutting down this lag phase between discovery and application.

Besides diagnostics, the obvious application of the fruits of the human genome project is the design of rational therapies aimed at correcting specific gene defects. This, of course, is no new idea and can be traced back to the 1940s when bacterial experiments were able to show the transfer of distinct traits from one bacteria to another. Granted, such early research did not even recognise the existence of DNA; however, such early lab work established the basis for gene transfer which by the summer of 2005 had advanced to the point whereby over 300 human clinical trials had been conducted in over 1,000 people to test the principle of correcting specific genetic disorders by attempting to beneficially alter the behaviour or sequence of human genes. Again, note the frustrating time lag.

In terms of ophthalmic applications, the delivery of a functioning RPE65 gene to dog models of the childhood blindness, Leber's congenital amaurosis (LCA), has been the most conspicuous success. Such success has provided valuable proof-of-concept for the potential application of such technologies in humans.

The Journal of Gene Medicine (2004; 6:597-602) has compiled many of the statistics on gene medicine trials run worldwide, two of which demonstrate the breakdown of types of diseases which to date have been the subject of clinical trials,

in addition to a breakdown of the progression of these trials through the various Phase I, II and III clinical trial stages.

Clearly, cancer has been the biggest target while the majority of trials are either in Phase I or Phase II with only 1% having made it into a full Phase III human clinical trial.

Evidently, there are significant hurdles to the translation of basic research into medical tools, not least among which is the cost, which brings us to the final “one to watch” over the coming decades.

Long journey from bench to bedside

At present taking a drug from “bench to bedside” can take anywhere between 10 and 15 years and cost hundreds of millions of euro.

However, as if the price were not high enough, industry must also manage the regulatory environment established to ensure public safety. Tension between the regulatory infrastructure and industry is natural within a high-stakes setting, and both sides have been burnt in recent years. One look at Merck and the 6,400 lawsuits facing it over Vioxx illustrate the face that drug development is not for the faint-hearted.

If the objective of the enormous effort that encompasses gene identification, drug development, and public safety is to be realised by providing tangible benefits to patients with inherited ocular disorders, then these three inter-disciplinary fields will need to become more cohesive, more streamlined, and more efficient.

Currently, according to the Pharmaceutical Research and Manufacturers of America, for every 5,000 medicines tested only one is eventually approved for patient use. Over the next few decades, all interested stakeholders will need to work together so that this ratio of success drops dramatically in favour of the patient.

Glossary

Complement factor H: a protein involved in the complement cascade, term referring to a cascade of biochemical reactions involving up to 30 proteins that function in immunity to cause the lysis of antibody coated target cells

Loci: a specific location on a chromosome which is occupied by an allele of a gene

RPE65: one of the genes which when mutated leads to a severe early childhood blindness known as Leber's congenital amaurosis