# Clinical Trials of Genetic Therapy with Antisense DNA and DNA Vectors

*edited by Eric Wickstrom*,
Marcel Dekker, 1998.
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Great medical advances are promised by the ongoing molecular biology revolution that has offered scientists and clinicians the exciting possibility of carefully manipulating individual gene expression in humans. Recent advances within molecular genetics have resulted in new therapeutic paradigms such as gene therapy, in which selected genes can be added to cells to restore the function of faulty or mutated genes and, more recently, antisense therapeutics, which aims to inhibit aberrant gene expression such as that of oncogenes or viral genes. Over the past decade, expectations within the medical and scientific communities with both of these technologies have been very high. However, it is fair to say that both forms of genetic therapies have endured 'roller-coaster' profiles of success and popularity. The initial promise and excitement resulting from successful demonstration of biological activity in cultured cells was invariably followed by difficulties in obtaining the same degree of success using animal models and in humans. During this roller-coaster ride, it became apparent that issues of safety, efficient delivery and expression or biological activity represented significant challenges to the successful clinical realization of these genetic therapies. Despite these obstacles, and with significant venture capital and government funding, both antisense and gene therapy have entered human clinical trials.

So, have antisense and gene therapy delivered their early promise? This latest edited volume by Eric Wickstrom aims to inform the readers of the latest developments within several of the ongoing clinical trials. *Clinical Trials of Genetic Therapy with Antisense DNA and DNA Vectors* is a timely addition to the literature as no previous volume has attempted to comprehensively review clinical trials data for antisense and gene therapy. However, if you read the book from cover to cover, you have to wait until the sixth chapter to get to the first results of a clinical trial. It is worth the wait though, as Erlinda Gordon and French Anderson expertly review the first-ever gene-therapy trials which aimed to correct severe combined immunodeficiency due to adenosine deaminase deficiency.

The book, however, begins with a brief but authoritative history of genetic therapy as seen by the founding editor of *Antisense and Nucleic Acid Development*, James Hawkins. This is a must-read chapter for a newcomer to the field or for anyone too busy to have kept pace with the rapid developments within gene-based therapies. The following four chapters deal with the regulatory and commercial-scale manufacturing of oligonucleotides and gene-therapy vectors and will be of great interest to industrial scientists and academics involved with the commercialization of genetic therapies.

The book thereafter is interspersed with chapters that detail example clinical trials and their associated pre-clinical studies with oligonucleotides and gene therapy for the treatment of blood-borne cancers such as leukaemia and lymphoma and of solid-tumours such as those of the lungs, brain, breasts, prostate and ovaries. All of these are fascinating reads but if you only had time to read one, I would recommend the chapter by Jack Roth. His chapter on the genetic therapies of lung cancer encompasses both the antisense and gene-therapy paradigms – a kind of 'two-for-the-price-of-one' offer. Lung tumours often express oncogenes such as k-ras but also exhibit loss of tumour suppresser genes such as *p53*. This trial aims to deliver a functional version of the *p53* tumour suppresser gene housed in a retroviral vector using direct local injections into the lung. In another protocol, Roth aims to inhibit expression of the mutant k-ras with a vector expressing antisense k-ras RNA. Although both trials are ongoing, three out of the seven patients receiving *p53* gene showed evidence of tumour regression in the treated lesions with some gene expression being evident in almost all patients treated. In addition, six out of seven patients showed evidence of tumour cells entering programmed cell death (apoptosis) – the ultimate goal of any cancer therapy. None of the patients were reported to undergo toxic effects directly attributable to the vector. Hence, these appear to be very encouraging results and we eagerly await the pending results of both trials and those of a possible future protocol where both paradigms are tested as a combination therapy.

The first antisense oligonucleotide to reach the market is a phosphorothioate molecule developed by ISIS pharmaceuticals. This compound, termed Fomiversen, is indicated for the treatment of cytomegalovirus-induced retinitis in AIDS patients and its progress in Phase III clinical trials is discussed in a chapter by Stanley Crooke. The editor has also included a chapter from Sudhir Agrawal of Hybridon highlighting the development of their compound GEM91 for potential anti-HIV applications. There is also a single chapter on the use of catalytic RNA (ribozymes) but this a prospective trial for the treatment of bladder cancer. There is no mention of the ongoing clinical trials with hammerhead ribozymes targeting HIV being conducted by John Rossi and Ribozyme Pharmaceuticals. This was the only surprising omission from this otherwise commendable volume.

The above-mentioned omission might have been symptomatic of a book that is probably just a little ahead of its time. The individual chapters provide a flavour of the ongoing clinical trials but because the trials are themselves incomplete, the reader is left waiting for the

complete picture. So, despite this fine contribution, it could take another volume to answer the widely asked question: 'have antisense and gene therapy delivered their early promise?' With genetic therapies predicted by many (myself included) to form the mainstay of disease control in the next millennium, there will undoubtedly be another opportunity for Eric Wickstrom to provide the complete picture. This volume has certainly whetted my appetite!

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## Neuroinflammation: Mechanisms and Management

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Multiple sclerosis is the archetypal disease of the brain and, for many years, meetings or reviews on neuroinflammatory disease were dominated by, if not wholly concerned with, discussion of multiple sclerosis and relevant animal models. In the past ten years this has changed. Neuroinflammation is of interest and concern to a diverse spectrum of basic and clinical neuroscientists, including those at the acute end of the disease spectrum studying neuroscience and head trauma, and those at the chronic end of the disease spectrum studying Alzheimer's and Parkinson's disease. It is interesting that the pharmaceutical industry has been as rapid to enter the arena as academic groups, and the significant contribution to this book by scientists from the industrial sector is testimony to this. There is a clear perception that this is an arena that will provide novel therapeutic targets in diseases for which effective treatments have yet to be found.

The inflammatory response in the brain is dominated in many circumstances by cells of the mononuclear phagocyte lineage and, in particular, the resident macrophages of the brain, the microglia. In no other organ of the body is there such intense interest in the contribution of the resident macrophages to inflammation, rather than the leukocytes recruited from the blood. It is apparent that macrophages can generate a plethora of inflammatory mediators, and so too can microglia *in vitro*. Wood provides extensive lists of receptors and secretory products expressed by microglia *in vitro*, and a few of these, especially components of the complement cascade (Walker, Rogers), and some cytokines (Martin) have been investigated *in vivo*. A clear message emerges that the microenvironment of the CNS imposes on the microglia a highly atypical macrophage phenotype. The normally quiescent microglia can be rapidly activated by a very diverse range of insults to the CNS, although what determines the mediators that the microglia synthesize under particular conditions is poorly understood.

A key question for those studying the atypical inflammatory response in the brain is whether the inflammation is a consequence of the disease, contributes to the disease, or is causal. It is clear that, in multiple sclerosis, inflammation is the cause of the disease, while in stroke (Kato) and Alzheimer's disease (Rogers and Griffin) there is evidence that the inflammatory response contributes to the outcome; the consensus opinion is that it contributes unfavourably. The mechanisms by which particular mediators contribute to the disease process are poorly understood. Although the actions of novel neurotoxins (Giulian and Li), nitric oxide (Boje) and eicosanoids (Rodger and Chan) are well studied *in vitro* and can be shown to be harmful to neurones, several authors highlight the need for data from good *in vivo* studies.

Few interested in neuroinflammation can fail to be aware of the importance of the trials with β-interferon in multiple sclerosis. These trials showed that inflammation in the brain in a chronic disabling disease was treatable and, at least in a proportion of patients, with significant benefit (Lechtenberg). The mechanism of action, however, remains to be defined. The relative lack of management of neuroinflammation is partly reflected in the fact that, while treatment of spinal cord injury with steroids (Hall) is discussed, as is β-interferon, these are the only two chapters given to the therapeutic issues. There is much to be done.

For those already working in the rapidly expanding area of neuroinflammation there is little that is new. The book might provide a useful reference source, but the rather limited index and the organization of references in each chapter, numbered in order of appearance in the text, are not user-friendly attributes. For those about to enter the field there are sufficient chapters in diverse areas that would make this a useful purchase but, at £110, not an essential one.

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