

Book Review

Viral Therapy of Human Cancers

Eds. Joseph G. Sinkovics, Joseph C. Horvath. 827 pages, 2984 references. Marcel Dekker, New York, 2005.

The first reports that virus infections may have a beneficial effect on cancer date back to the end of the 19th and the beginning of the 20th century. However, initial deliberate attempts to utilize viruses as oncolytic agents in the treatment of experimental tumours in animals or in clinical studies were only undertaken several decades later. By then it was possible to draw upon findings that some viruses reproduce better in tumour than in non-tumour cells; nevertheless, no significant success was reported. A big renaissance of the endeavour to make use of viruses for the treatment of tumours came towards the end of the 20th century. Conditions for this were set by the new knowledge on the molecular biology of viruses, by the developments in genetic engineering and gene therapy, as well as by the substantial progress in immunology. Viral therapy of cancers thus acquired a respected position on the contemporary medical scene.

The editors of the book, who are also its main authors, have together with their co-authors undertaken to sum up the up-to-now results of the endeavours to achieve viral therapy of cancers, as well as to critically appraise the present situation. They are concerned with either of today's lines of approach to the utilization of viruses in tumour treatment, viz.: (1) that based on the direct oncolytic effect of certain viruses, which is due to a selective sensitivity of cancer cells to them, and (2) the use of modified viruses as vectors for the import of foreign genes (transgenes) into tumour cells. Depending on the character of the transgenes, the cancers become either strongly immunogenic or highly sensitive to specific chemotherapy (e.g. with the help of so-called suicide genes), or they lose their malignant phenotype. The authors devote most space to point (1), i.e. to oncolytic viruses. This term refers to viruses which, owing to their natural biological properties or because they have been genetically manipulated, reproduce well in cells with an oncogenic potential but do not reproduce at all or only on a very limited scale in non-tumour cells. The authors describe the concepts upon which the employment of different viruses for the destruction of cancer cells is based, but they also discuss in detail the setbacks (e.g. the potent immunogenicity of viruses) that complicate their clinical use. Ideas and plans how the systems available might be improved form substantial parts of the individual chapters and make the most inspiring reading.

The book consists of 13 chapters and an epilogue. The most informative are the first two chapters, written by J. G. Sinkovics. They make over a half of the entire

text and contain everything essential for understanding the general principles of viral therapy of cancers and the specific problems associated with the individual viruses. The subject of the first chapter is adequately characterized by its title: *Progressive Development of Viral Therapy. A Personal Narrative Account*. Its author was one of the first researchers who started work with oncolytic viruses. He carried out his first study with these viruses nearly 50 years ago in his native Hungary, and over the subsequent decades he followed and himself pushed forward their investigation. Thus, he is eminently qualified to present a historical review. The chapter briefly characterizes the viruses that today represent the main candidates for oncolytic agents and describes the problems involved in the transfer of results obtained in studies performed *in vitro* or in xenogenic systems into clinical practice. Chapter 2 (*New Biological Therapeutics: Competitors or Collaborators of Viral Therapy for Human Cancers*) summarizes the principal characteristics of cancer cell biology and, in particular, describes the biochemical pathways whose activation is responsible for the development of the malignant phenotype. Attention is called to the possibility that chemotherapy, which deranges these pathways, may interfere with the oncolytic effect of viruses. Further discussion is devoted to ways in which the oncolytic effect of viruses could be enhanced. The author emphasizes that problems connected with the employment of viruses for tumour therapy cannot be resolved without deep knowledge of cancer cell biology and of cancer pathogenesis and that one should allow for the differences between cancer cell populations studied *in vitro* and in a cancer growing in a living organism. He stresses that it is necessary to perfectly know the manner of replication of any virus if one is to make use of its selective effect on cancer cells. I dare not judge the completeness of the material presented, but it certainly commands respect by its richness, by the opportuneness of the questions it raises, as well as by the adequacy of the ideas proposing solutions to actual or possible problems.

The text also calls attention to the interrelations between the use of oncolytic viruses and the development or potentiation of the anti-tumour immunity of the organism. This idea is developed in detail in further chapters. The author also mentions some of his early original observations, which came ahead of time and did not arouse the attention they deserved, possibly only because they were not further elaborated right then and were not described in the language that later came to be used. For instance, this relates to the discovery of

so-called "natural hybridomas", i.e. fusion cells that permanently produce antibodies.

Further chapters are devoted to the individual viruses. Chapter 3 (*Measles Virus: Improving Natural Oncolytic Properties by Genetic Engineering*, by C. Springfield et al.) describes the efforts to improve the present properties of the measles virus for cancer therapy. The subject of Chapter 4 (*Antitumor Immune Memory and Its Activation for Residual Tumor Cells and Improvement of Patients' Survival: A New Concept Derived from Translational Research with the Virus-Modified Tumor Vaccine ATV-NDV*, by V. Schirmmacher) is the construction of anti-tumour vaccines based upon cells infected with Newcastle disease virus (NDV). Together with the results adduced, the author presents an interesting concept of the development and maintenance of anti-tumour immunity and accords attention to the relations between the presence of memory cells and so-called dormant tumour cells. The NDV virus and the various aspects of its anti-tumour effect are treated in Chapter 5 (*Newcastle Disease Virus: Its Oncolytic Properties*, by J. C. Horvath). The author enlarges on the uses of NDV in the therapy of tumours. He explains the selective effect of the virus on tumour cells in much detail and offers some new hypotheses, which he is prepared to verify. The subsequent three chapters (6, *Influenza A Viruses with Deletions in the NSI Gene*, by M. Bergmann and T. Muster; 7, *Vesicular Stomatitis: An Oncolytic Virus that Exploits Tumour-specific Defects in the Interferon Pathway*, by R. A. C. Taylor et al., and 8, *Parvoviruses as Anticancer Agents*, by J. Rommealere et al.) treat the abilities of the respective viruses to produce oncolytic effects and of the chances of their utilization in future. A part of Chapter 6 is devoted to reoviruses, which recently, thanks to their unique properties, have been attracting rising interest as possible oncolytic agents. The next two chapters (9, *Newcastle Disease Virus Oncolysates in the Management of Stage III Malignant Melanoma*, by W. A. Cassel et al., and 10, *Vaccinia Viral Lysates in Immunotherapy of Melanoma*, by P. Hershey) present, besides basic characteristics of the viruses used, the results of some clinical studies with therapeutic anti-cancer vaccines based on viral lysates of cancer cells. The effectiveness of the therapy differed between the studies, which was most probably due not only to the characteristics of the individual viruses used, but also to the different ways of vaccination and evaluation of results. Herpesviruses belong among the most favourite oncolytic viruses and their mutants have already been used in human cancer therapy. Detailed descriptions of the biological properties of the viruses tested and of some new mutants based on other principles, as well as the experience gained with their investigation, constitute Chapter 11 (*Fusogenic Oncolytic Herpes simplex Viruses for Therapy of Solid Tumours*, by X. Fu et al.). The next chapter (12, *Poliovirus Recombinants against*

Malignant Glioma, by M. Merrill et al.), which is one of the best written parts of the book, is concerned with the use of poliovirus recombinants for cerebral cancer therapy. It gives a very well presented, deep insight into poliovirus biology, which makes clear the reasons for the utilization of these viruses. The last chapter (13, *Oncolytic Viruses that Depend on Loss of RB or 53*, by F. McCormick) substantiates and describes research with viral mutants that are capable of replicating in tumour cells because this has been made possible by those genetic defects of the cells that have made them acquire the malignant phenotype.

The editors have given the authors freedom in organizing their respective chapters. Accordingly, their structure varies considerably, nevertheless the basic lay-out is similar. All chapters begin with detailed characterization of their particular viruses, all pay attention to the biology of the tumours to be treated, sum up the findings on the oncolytic effect of the viruses in cell lines derived from the particular types of cancer and in cancers in xenogenic systems, characterize the advantages and disadvantages of the viruses chosen, consider the possibilities of enhancing their effectiveness and safety, emphasize their capability of raising the antitumour immune responses and finally present the results of the first clinical studies if already available. The chapters sometimes overlap by their content, but this is unavoidable, while the repetition of some basic findings and concepts is not detrimental. All authors without exception stress the advantages of "their" virus, but this should not be criticized, for precisely the recognition of these advantages accounted for their choice. All facts are presented with considerable criticism, with awareness of the shortcomings of the present systems and possible risks involved in their application. These include potential mutations of the viruses, their recombination with wild viruses, but also the liberation of cytokines, which might support tumour growth. The chapters show differences in the philosophy of the different research groups, which are projected into the strategy of the research. The book closes with an Epilogue (*Damn the Torpedoes! Full Speed Ahead!*), whose authors are J. G. Sinkovits and J. C. Horvath. In spite of its dramatic title, the tuning of the Epilogue is sober and highly disciplined. It gives an overview of the whole subject, formulates with clarity the problems that must be resolved, and makes it clear that the use of viruses in cancer therapy is a gradual process which is interconnected with the continuing cognition of the biology of cancer cells and of the viruses themselves, as well as of the immune processes going on in the organism being treated. The authors specify the most promising areas of contemporary research, among which they include the endeavour to develop a gene-based therapy of tumours. They emphasize the need to have a balanced combination of viral therapy of cancers with other types of cancer treatment and especially its inter-

connection with cancer immunotherapy. The Epilogue culminates in an expression of the conviction of the editors of the book that biological therapies are bound to play a significant role in the treatment of malignant tumours in the not very distant future.

As a criticism, I would reproach the authors of the book for an excessive use of abbreviations. If the work comes out in a second edition, I suggest it should include a list of the abbreviations used, and commendably also a glossary of the terms that are not quite familiar to clinical oncologists. It will be they who will form the majority of its readers.

The authors have succeeded, as far as I am aware, in compiling a book unique in its overall purport and arrangement. It is bound to very substantially raise the informedness of oncologists about the potentialities of viruses used as agents capable of *in vivo* liquidating

cancers or at least retarding their progression, as vectors for the transfer of genes whose presence in cancer cells will improve the prospects of therapeutic success, or as promising agents for the preparation of therapeutic anti-cancer vaccines. The book presents an unusually large number of references, which will provide the reader with detailed information about the authors' literary sources. The work may be recommended to all who would like to learn more about the new, progressive methods of cancer therapy.

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