Monoclonal Antibodies and T-Cell Hybridomas

Perspectives and technical advances

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1981
ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS
AMSTERDAM · NEW YORK · OXFORD

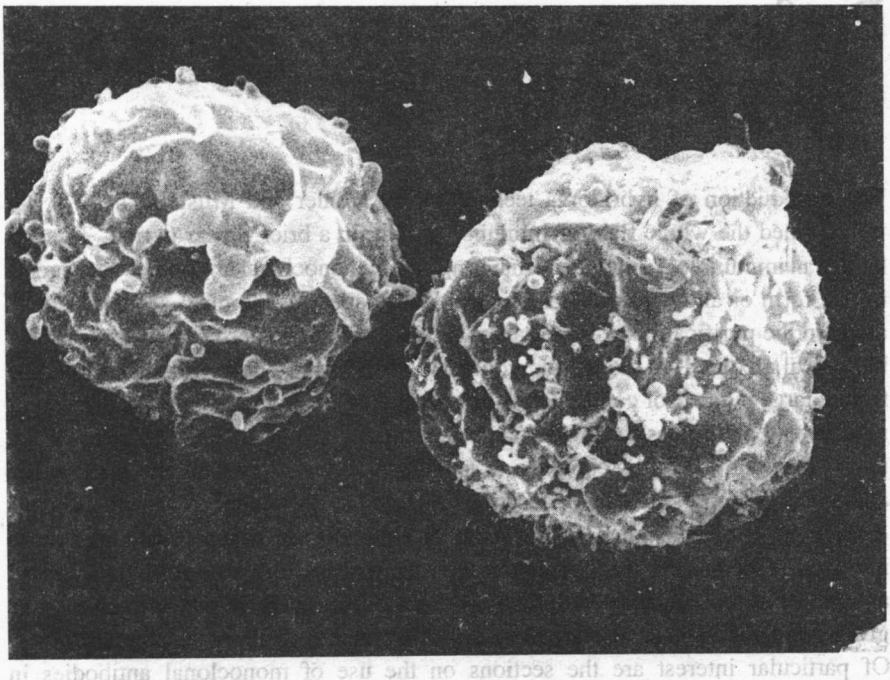
Preface

The introduction of hybridoma technology by Köhler and Milstein in 1976 has transformed the whole field of Immunology within a brief 5 year period. There is hardly an immunology laboratory that is not using monoclonal antibodies as reagents in one form or another, whether it is to identify specific chemical groupings or to assist in the purification of important molecules, such as interferon, from complex biological mixtures. In the present volume the editors provide a composite expertise from a large number of colleagues with a breadth of experience in the production of monoclonal antibodies to a wide range of antigens. These include antigens of the major histocompatibility complex of man and rodents, as well as other tissue antigens. An important section describes reagents to detect and react with antigens derived from human tumours. Monoclonal antibodies to tissues other than those involved in neoplastic transformation are also discussed. The use of monoclonal antibodies in the diagnosis of infectious diseases, particularly parasitic disease, is given good coverage as also are monoclonal antibodies to allergens and hormones. Of particular interest are the sections on the use of monoclonal antibodies in analysing immunological phenomena themselves, particularly aspects of idiotypic expression and interactions. The production of monoclonal antibodies by human hybridomas is also covered in a useful manner.

T-cell hybridomas are a major advance for those working on T-cell function. This breakthrough has provided the key to the availability of T-cell products, both helper and suppressor factors. Without this technical advance it would have been impossible to obtain these products in a sufficient state of purity for any degree of accurate chemical characterisation.

It is hoped that this volume will provide a useful introduction to the spectrum of uses to which this new technology can be applied, and will become an important addition to departmental libraries. The commercial importance of monoclonal antibody technology has been recognised at a number of levels, not least of which is governmental. Thus, in the next five years even wider applications will be discovered for this major conceptual and technological advance. As much of the information available in this volume is scattered throughout the literature, I believe that this collection of reviews from those currently working in the field will prove a valuable volume to those about to enter this important field of research, as well as to those involved themselves in advancing the field.

J.L. Turk
April 1981



Human hybridoma cells. Derived from fusion of the human myeloma line GH.U266.8-1.6 with human peripheral blood lymphocytes. Magnification 20,000 ×. Courtesy of Drs. Komitowsky and Hämmerling, German Cancer Research Center, Heidelberg.

Introduction

The epic drama of the Heike of ancient Japan narrates the rise of a powerful clan and its demise at the hands of a rival clan. It is a tale of brave warriors as well as of cowardice, of trust and treachery, of pride and vanity. But above all it depicts a man who, despite his helplessness to shape his own destiny, ultimately transcends and achieves immortality through his faith in the future. This transcendence over earthly impermanence is symbolized by the suicide of the child-prince, who seeing the final battle lost throws himself into the sea. The philosophical message for us scientists can be or should be the warning that achievements and progress are often of short duration and that we have to thrive towards permanency. The legend of the Heike has been part of the Japanese folklore for centuries, and has produced a most curious result which may be of interest to science. The fishermen conscious of the possible reincarnation of the drowned Heike prince have regularly returned those crabs to the sea which bore the image of a samurai on their shell, and it is said that the artificial selection by man has led to an abundance of this particular, commercially inferior, strain of crab.

The themes of transcendence, immortality and selection which pervade the saga of the Heike, may also incite the mind of Immunologists, because many of us feel that something of this kind has happened in Serology. The evolution of serology from an initially specialized typing procedure to a laboratory procedure practiced almost ubiquitously in Biology and Medicine is punctuated by a number of discoveries. For instance, tissue typing techniques depended initially on crude heteroantisera, the specificity of which was refined by sequential absorptions, as knowledge grew of the serological individuality to tissues. Thus the original antibody mixtures were divided into progressively smaller and at the same time more specific fractions. A decisive leap forward was the introduction of alloimmunizations because now the spectrum of antibody formation could be restricted for genetic reasons. These techniques led to the establishment of the discipline of Immunogenetics which plays an increasingly important role in many fields, e.g. in Cancer Research. The next logical development was the introduction of congenic strains of mice which allowed the production of closely, albeit not absolutely, monospecific antisera. It is in the nature of the immune response as basically a mechanism of selection by antigen and of initiating expansion of qualified lymphocytes which then secrete their predetermined antibody that truly

monospecific antisera cannot be obtained except by cloning of individual B cells. Thus, it may rank as a revolutionary development that such cloning became possible, and it became possible by overcoming the intrinsic proliferative restrictions of normal plasma cells, by implantation of the potential for the indefinite division of a tumor cell. As a consequence, the plasma cell was transformed into a tumor, and it is this transformation that echoes the element of transcendency because it changes the life-threatening property of a tumor to a life-giving one. Undoubtedly, the credit for this revolutionary feat should go to George Köhler and Cesar Milstein who produced the first antibody secreting hybridomas, and also to those scientists who recognized the importance of plasmacytomas as Immunology's *E. coli* and established these firmly as invaluable research tools.

In compiling this book we felt that the scientific community would be best served by presentations of recent achievements that could reflect kaleidoscopically the current state of the art. Needless to say that the invitations issued to contributors were a subjective selection, and it was neither our intention to give a complete overview, nor would this be physically possible in a single volume. The papers were invited as mere examples of the dynamic, almost explosive expansion, of hybridoma research into several areas of Biology and Medicine. The rapid changeover from conventional antisera to monoclonal antibodies in areas traditionally depending on serological techniques, e.g. immunogenetics of experimental animals and man, comes as no surprise, but the detail of knowledge generated in a brief time is indeed stunning.

We experience today a veritable inflation of information which will cause us to revise the nomenclature of several of the familiar antigenic systems as well as to add new ones to the list, and it is quite possible that we may have to rethink some of the concepts underlying the structural, biochemical and genetic relationships between tissue antigens. In the final analysis some immunogenetic questions may have very simple answers. For instance, years of work spent on the elucidation of the H-3 locus of mice and surface antigens associated with this locus may yield the almost trivial answer that they all are the same entity and furthermore that they are reflections of polymorphism of a well-known component, β_2-microglobulin.

An equally important and inflationary flow of data is in store for us in Bacteriology and Virology. Clinical serologists may have to relearn in part their classification systems. Whereas these developments in microbiology were predictable, the advances in serology of parasites are truly astonishing and they raise justified hopes to generate more definitive diagnostic procedures, and possibly of vaccines. Similarly, improvements of tissue typing techniques will have their impact on the clinic. For instance, a more precise classification of tumors as for instance imminent for leukemias, will lead to more accurate prognoses and to more rational selection of treatment modalities. As regards the therapeutic use of monoclonal antibodies, there are numerous practical applications possible in the field of infectious diseases, awaiting,

however, the development of human monoclonal antibodies. Immunotherapy of tumors is still doubtful in spite of some isolated reports that tumor regression can be initiated. But to remain optimistic it may be well to remember that chemotherapy also initially did not accomplish more than a modest increase of survival lines.

In addition, monoclonal antibodies to hormones and other physiologically relevant factors prove already now to be extremely valuable tools not only for classification, diagnostic purposes and exact quantitation of factors, but also for efficient separation and isolation of rare substances.

Needless to say that monoclonal antibodies have contributed very much to advances in many other areas of Medicine and Biology, such as studies on the origin of antibody diversity and the immune network, and others. But hybridomas need not be restricted to antibody production. Thus a large number of T-cell hybridomas has been prepared during the last few years which secrete a variety of factors, such as helper and suppressor factors which are of crucial importance for the regulation of immune reactions. It is hoped that these factors can be employed for manipulation of immune responses as well as for biochemical and structural work, although it has to be stated that so far the availability of T-cell hybrids did not considerably increase our fragmentary knowledge of the chemical structure of T-cell factors, which may be due to an almost notorious instability of T hybrids and to a low production rate of factors.

Similarly to hybridomas one can also envisage the immortalization by cell hybridization of other biologically important cells for the manufacture of other natural products. Finally, in conjunction with the recombinant DNA technique, which is the other powerful bio-technique developed during the last decade, cell hybrids and monoclonal antibodies can be valuable and complementing tools for genetic engineering and mass production of natural substances by *E. coli*.

Beyond giving a perspective of hybridoma research this book is also meant to give practical help for the derivation of antigen-specific hybridoma lines. Thus, a set of practical recipes has been included and this may be helpful to get the novice to the field started. Evidently, special applications of hybridoma research will require modifications to suit the purpose. In this regard helpful hints can be extracted from the individual contributions to this book. This was the reason for our attempt of a wide coverage of topics, and if successful practical help derives from it, this book would indeed serve a good purpose.

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