THE APPLICATIONS OF MONOCLONAL ANTIBODIES IN PAEDIATRIC ONCOLOGY

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By

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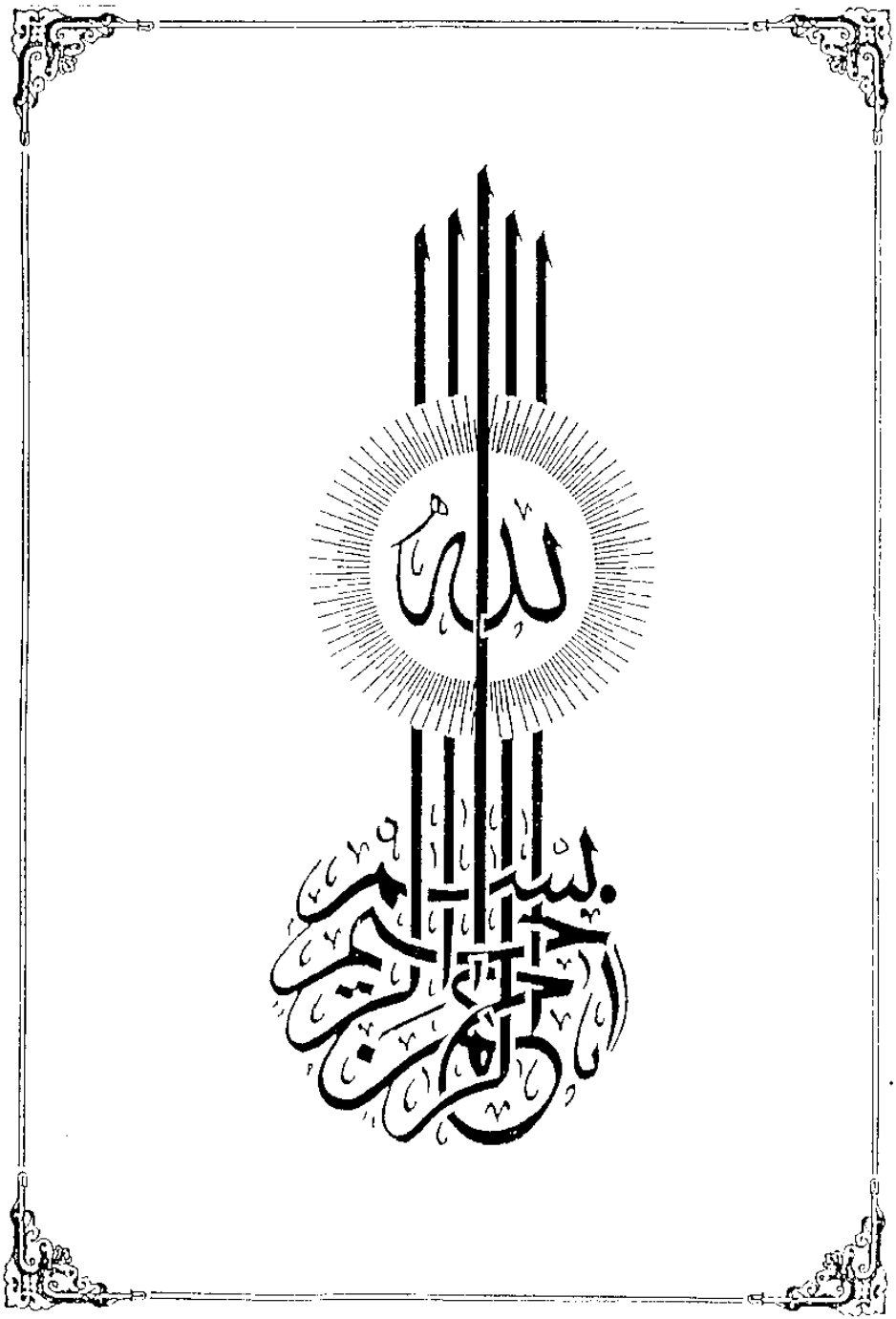
بسم الله الرحمن الرحيم

" قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم "

صدق الله العظيم آية ٣٢ سورة البقرة



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C O N T E N T S

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ab	:	Antibody
ABMT	:	Autologous bone marrow transplantation
ADCC	:	Antibody dependent cell mediated cytotoxicity
Ag	:	Antigen
ALL	:	Acute lymphoblastic leukaemia
AML	:	Acute myeloid leukaemia
ANLL	:	Acute non-Lymphoblastic leukaemia
B-ALL	:	B-cell acute lymphoblastic leukaemia
C_3	:	Complement 3
CALLA	:	Common acute lymphoblastic leukaemia antigen
CD	:	Cluster differentiation
CIg	:	Cytoplasmic immunoglobulin
Cu	:	Cytoplasmic u-heavy chain
EBV	:	Epstein Barr virus
FAB	:	French - American - British
FACs	:	Fluorescence activated cell sorter
HAT	:	Hypoxanthine, aminopterin and thymidine
HCs	:	Hodgkin's cells
HD	:	Hodgkin's disease
HLA	:	Histocompatibility antigen
HPRT	:	Hypoxanthine phosphoribosyl transferase
Ig	:	Immunoglobulin
Kd	:	Kilo dalton

LL	:	Lymphoblastic lymphoma
MAb	:	Monoclonal antibody
MF	:	Mycosis fungoides
NB	:	Neuroblastoma
NSE	:	Neurone specific enolase
PAbs	:	Polyclonal antibodies
RSCs	:	Reed-Sternberg cells
SmIg	:	Surface membrane immunoglobulin
T-ALL	:	T-cell acute lymphoblastic leukaemia
T B	:	B subunit of T-cell receptor antigen
TdT	:	Terminal deoxynucleotidyl transferase
TL	:	Thymic leukaemia.

- I -

INTRODUCTION

The immortalization of specific antibody-producing cells, first reported by Kohler and Milstein, in 1975, rapidly led to widespread application of monoclonal antibodies (MAbs) in research laboratories and in clinical diagnostic medicine. The Nobel prize in medicine was recently granted for this work (David and Gordon, 1985).

MAbs are identical antibodies with the same binding specificity that can be generated in unlimited amounts by construction of continuous cultures of single Ab-secreting cells. These cell lines are produced by cell fusion of lymphocytes of an animal that produces desired Ab to cells of a myeloma tumour cell line, which confers, on the Ab-producing hybrid cell, immortality and the ability to grow as a tumour in animals. The Abs are replacing conventional polyclonal antisera in immunologic assays and are being widely applied to the study of the pathogenesis and to the diagnosis and treatment of childhood diseases (Richard et al., 1983).

The advent of monoclonal technology has been followed by a stream of reports of tumour-associated antigens with diagnostic or therapeutic potential. Most such reports have arisen from the empirical practice of raising large numbers of Abs against tumour cells and then screening each Ab for its reactivity with a range of tissues. Any Ab showing a potentially useful specificity can be selected for bulk preparation without knowing anything about the target antigen apart from its apparent tissue distribution. The greatest number of such Abs have been raised against leukaemias and lymphomas (Glennie and Stevenson, 1985).

- II -

GENERAL CONSIDERATIONS

A major focus for cancer immunologists has been the identification of cell-surface Ags that are uniquely expressed by tumour cells. Historically, the most objective approach used to define Ags expressed by human malignant cell surfaces has been to develop hetero-antisera by immunizing animals with malignant cells (Bernstein et al., 1985).

Tumour cells, like normal cells have innumerable cell surface antigenic determinants, including those on receptors, histocompatibility molecules, blood group molecules, and differentiation molecules. Although not absolutely tumour-specific, some of these determinants are expressed by few types of normal cells and may therefore serve as operationally specific markers for tumour diagnosis and therapy (Seeger et al., 1982).

What is a monoclonal antibody ?

The immunological response to any foreign antigen is polyclonal : many different clones of B lymphocytes are stimulated to produce Abs. These Abs have different molecular structures and in turn recognise different

molecular conformation patterns on the stimulating antigen; the antigenic determinants. MAbs occur naturally in patients with multiple myeloma. Here neoplastic transformation occurs in a clone of B lymphocytes with the result that large quantities of identical Ig molecules are produced. It was by using myelomas that the chemical structure of the Ig molecule was discovered (Sikora, 1982).

Production of MAbs : (Fig. II-1 and Fig. II-2)

Mice are immunized with Ag by the intraperitoneal or I.V. route to induce a primary antibody response. After an interval, the animal is reimmunized and 3 to 4 days later, the mouse is killed and splenectomized; the spleen cells are then collected.

A suspension of the spleen cells is incubated with a suspension of murine myeloma cells in the presence of polyethylene glycol, an agent that promotes cell fusion (Kohler and Milstein, 1975). Activated spleen cells preferentially fuse with myeloma cells. The number of hybrids formed by cell fusion is few in comparsion with the number of myeloma cells.

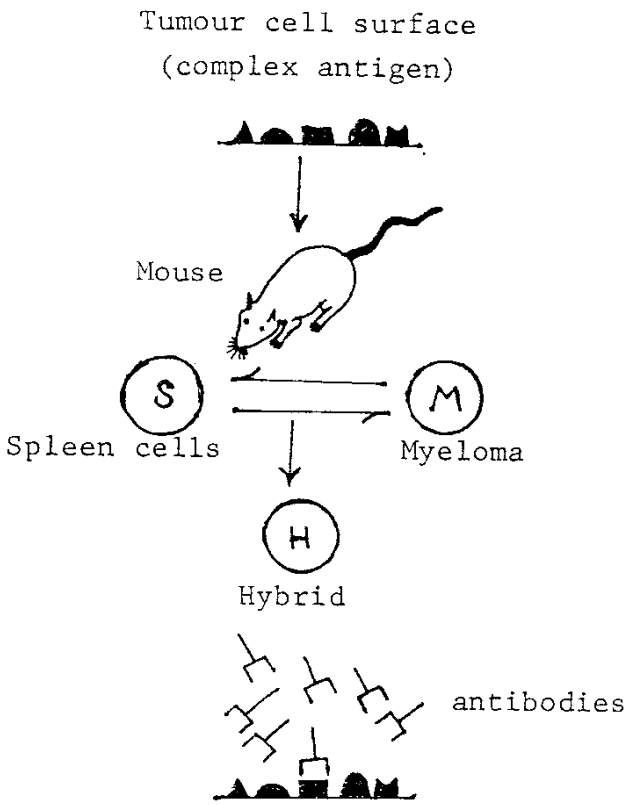

Fig. II-1. Making a monoclonal antibody. A complex antigen, such as a tumour cell surface, is used to immunise mice. The spleen cells(s) are removed and fused with a myeloma line (M). Hybrids are cloned and those antibodies binding to the antigen selected (Sikora, 1982).