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Book Review

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Immunodeficient Animals: Models for Cancer Research
Editors: W. Arnold, P. Köpf-Maier and B. Michael
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GIVEN THE rapid progress of *in vitro* and cell-culture based biomedical research, animal models which allow the extension of these studies *in vivo* have become increasingly important. These models include transgenic or 'knock-out' animals, which allow *in vivo* functions of individual genes to be tested, as well as sophisticated xenotransplant models for the study of normal or diseased human cells in an *in vivo* situation. Many of these xenotransplant models use immunologically incompetent hosts. The use of murine xenograft models in cancer research is the topic of this book, which is based on a Workshop on Immunodeficient Laboratory Animals held in Berlin in October 1993.

An overview of the workshop is given by short articles of 4–6 pages written by workshop participants. Articles cover individual contributions and are grouped under the main sections, 'biology of the mutants nude, scid and mu', 'development of xenotransplantation systems for human tumors', 'use of xenotransplant systems to evaluate chemotherapy, radiotherapy and immunotherapy approaches', 'chances and limitations of *in vitro* methods as alternative models'.

Breeding modalities, immunological properties of mutant strains, spontaneous tumour occurrence in immunodeficient mice, thermoregulation and thymus dysgenesis are dealt with in the first section. In addition, two xenogeneic non-cancer models are discussed. The survival of human thyroid tissue in nude mice and its modulation by high-dose iodine and cytokines are described, as well as the use of scid recipients to monitor gene expression in genetically modified human arterial segments.

The second section of this book introduces xenotransplant models for human tumour cell lines and primary tumour specimens. These models cover prostate, ovarian, thyroid gland, hypopharynx, lung and renal cancer. In addition, technical aspects of these models, such as the site of implants, the diet of animals or the use of primary versus metastatic tumour tissue, are discussed. This section is supplemented by data on the secretion of tumour markers by human xenografts, and by biodistribution studies for radiolabelled antibodies in immunodeficient animals, with a specific focus on antibody availability at the site of the xenograft.

The third section covers the use of xenotransplant models for preclinical evaluation of novel chemotherapy, radiotherapy or immunotherapy regimens. Long-term results obtained by the Amsterdam and Freiburg groups in the EORTC antitumour screening programme are presented, as well as breast cancer xenograft studies on the tumour inhibitory effects of ascorbic acid, alkylphosphocholines, or hormone treatment, and studies in a malignant melanoma model on regional chemotherapy, with hyaluronidase plus vinblastine. In addition, studies are presented on current problems in radiation therapy, such as endogenous alpha-irradiation therapy in thyroid cancer and the use of radiosensitisers in large bowel cancer. Immunotherapeutic approaches cover treatment strategies for Hodgkin's disease and disseminated neuroblastoma. Also included in this section are two articles reporting on the transfer of functional human haematopoietic cells or bovine immune cells into scid mice. Given the lack of adequate *in vitro* assays for very early stages of haematopoiesis and the complex interactions underlying the development and function of the human immune system, these models may have broad implications in the field of experimental haematology and immunology.

The fourth section of the book describes *in vitro* systems and their capabilities and limitations as alternatives to animal models. This part mainly deals with improved methods of tumour cell cultivation and the use of these cultures to test tumour chemosensitivity. In addition, culture methods for embryonic stem cells are discussed.

All contributions are written in the classical style of scientific papers consisting of Introduction, Materials and Methods, Results and Discussion. In most cases, a summary (abstract) is provided. Articles are written in a concise and easy-to-understand style, and the 88 figures and 38 tables of the book help the comprehension of the data presented. However, there is only a short general introduction to the book, and no summaries or commentaries are given on individual sections. This allows individual authors to summarise their work and highlight what they feel are important aspects, but, without considerable background information, it is difficult to evaluate the relevance of individual studies and to put these into perspective with other work in the field. Therefore, the book is of limited use to newcomers to this area of research.

Those who should profit most from this publication are researchers already familiar with the field, but in need of gaining additional information on specific models. As such, it is helpful that some of the papers carry an extensive bibliography with up to 40 references. However, timing of the publication presents a problem. Nearly 3 years after the workshop many of the systems described here have advanced considerably and some of the information presented here no longer represents the actual standard.

In summary, this volume offers information on xenotransplant systems based on immunodeficient mice, relevant mostly to researchers in the same or related areas of research. In this respect, the book is well-written and equipped with important and specific data. The time of

publication (3 years after the workshop), however, may limit its value as an up-to-data reference book.

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Letters

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Vasoactive Intestinal Polypeptide (VIP) and Neuropeptide Tyrosine (NPY) in Prostate Carcinoma

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UP TO 50% of all prostate carcinomas contain neuroendocrine (NE) differentiated cells secreting serotonin and/or regulatory peptides [1]. Abrahamsson and associates were the first to examine systematically the occurrence of NE differentiated cells and their peptide and biogenic amine content both in normal, hyperplastic and neoplastic glands [2]. We report the presence of two neuropeptides not yet reported in prostate carcinoma cells.

Tissue specimens from 20 cases of prostate carcinoma (average age 65 years, range 52–78 years) were obtained from radical prostatectomy operations. They were routinely fixed in neutral 4% phosphate-buffered formaldehyde. Paraffin sections 5 μm thick were adhered to APES (aminopropyltriethoxisilane)-coated glass slides. Haematoxylin and eosin staining was used for routine histopathological examination and tumour grading, according to Mostofi [3].

Tissue sections from representative areas of the peripheral zones of the carcinoma were immunostained for NE markers, i.e. chromogranin A (CgA), synaptophysin, neuron-specific enolase (NSE), and protein gene product 9.5 (PGP-9.5), to screen for NE differentiation, and for a series of neuropeptides using the streptavidin–biotin–peroxidase complex (S-ABC) and the immunogold–silver staining (IGSS) method with silver acetate autometallography [4, 5]. Antigen retrieval techniques were applied using microwave irradiation or autoclaving [5, 6]. Specificity tests also included absorption controls carried out on antibodies to peptides with immunologically related synthetic peptides in concentrations of 10 nM and 100 nM per ml of optimally diluted primary antibody. Analysis of staining results included differentiation between parenchymal cells in apparently normal and hyperplastic areas (as defined by nodularity of the parenchyma), as well as in carcinoma, all of which were sometimes present within the same large tissue section (on average 2–3 cm in diameter).

CgA immunoreactive carcinoma cells were found in 15 cases (75%), NSE in 17 cases (85%), synaptophysin in 6 cases (30%), and PGP-9.5 in 10 cases (50%). Cytoplasmic labelling of scattered, sometimes even numerous, tumour cells was obtained with antibodies to vasoactive intestinal polypeptide (VIP) in 10 cases (50%) and to neuropeptide tyrosine (NPY) in 15 cases (75%). 7 cases expressed both NPY and VIP, sometimes even in the same tumour cells. It was found that most cases expressing either VIP and/or NPY also expressed CgA, PGP-9.5 and NSE, and a few also expressed synaptophysin. However, one VIP-immunoreactive carcinoma did not show any of the broad-spectrum NE markers investigated. In all other peptide-immunoreactive cases, at least one of these general markers was positive.

Other peptide antisera applied, such as peptide histidine methionine (PHM), prepro-vasoactive intestinal polypeptide (prepro-VIP), somatostatin, substance-P, helodermin, helospectin, galanin, bombesin, met-enkephalin, and calcitonin gene-related peptide (CGRP) gave no immunostaining.

CgA-immunoreactive parenchymal NE cells were found in approximately three-quarters of the cases containing hyperplastic and normal areas, and PGP-9.5-immunoreactive NE-differentiated cells were found in one-third of those containing hyperplastic areas, but only in one containing normal glandular areas. NSE-immunoreactive cells were not detected in normal parenchyma, but in 10% of cases containing hyperplastic glandular areas. No synaptophysin immunoreactivity was found. NPY-immunoreactive cells were not present in normal areas, but in one case containing hyperplastic areas. VIP-immunoreactive cells were rarely present in the surrounding normal glandular tissue (one case), but was demonstrated in one-third of cases containing hyperplastic areas.

A number of studies have revealed that NE differentiation in prostate carcinomas occurs frequently [1, 2, 7–9]. In prostate hyperplasia and carcinomas, immunostainings for calcitonin, CGRP, bombesin, somatostatin and thyroid stimulating hormone have been demonstrated [1, 2]. In our study, NPY and VIP cells in prostate carcinoma were detected.

NPY immunoreactive material is usually found in the central and peripheral nervous system in noradrenergic neurons and nerves [12]. There it functions as a vasoconstrictor, increasing the actions of noradrenalin, and this peptide is considered to be a putative neurotransmitter. In the

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