Current Status of Medical Biotechnology in Malaysia

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In recent years medical research, utilising biotechnology and related tools, has contributed significantly to advances in the laboratory diagnosis of infectious diseases and hormonal disorders in Malaysia.

The main thrust was in the development of diagnostic assays or kits, either for import substitution or to meet diagnostic needs for diseases of importance. Emphasis was on the development of diagnostic probes either using the hybridoma technology for the production of monoclonal antibodies (MABs) or the development of nucleic acid probes. In other instances, conventional techniques for the production of polyclonal antibodies and their subsequent radiolabelling for radioimmunoassays were carried out. The applicability of polymerase chain reaction (PCR) in the development of rapid and specific diagnostic assays was investigated.

Examples of research utilising conventional as well as newer techniques were those in viral diseases like dengue, dengue haemorrhagic fever, Japanese B encephalitis, and Hepatitis B virus. A mosquito larva inoculation method was developed and refined for the rapid isolation (4 days) of dengue virus. An IgM capture ELISA using monoclonal antibodies was found to be useful for the early diagnosis of dengue infection. A similar test using cell culture derived dengue antigens and a polyclonal rabbit antiflavivirus antisera, and a dot enzyme immunoassay for the detection of dengue were also developed. The former test is useful for the detection of primary infections while the latter can be used to detect secondary infections. Similar IgM capture ELISA and dot blot assays were developed for Japanese B encephalitis infection. An in-house assay based on a modified double sandwich ELISA was also developed for the detection of HBsAg.

In bacterial diseases, typhoid and other salmonellosis were studied. A dot blot ELISA based on a specific 50 kDa outer membrane protein of Salmonella typhi was developed for the detection of specific IgM and IgG antibodies for the rapid diagnosis of typhoid.

For parasitic infections, malaria, filariasis, toxoplasmosis, toxocariasis and angiostrongyliasis were studied. The emphasis was to develop immunodiagnostic assays for patient diagnosis and epidemiological assessment. Most of these immunodiagnostic assays are not commercially available (angiostrongyliasis, filariasis, toxocariasis) or extremely expensive (toxoplasmosis, malaria). The indirect fluorescent antibody assay (IFA) for the diagnosis of filariasis, malaria and toxoplasmosis and the ELISA for toxocariasis were developed and are routinely being used. ELISA assays based on various stage-specific antigens were also developed for seroepidemiological assessment of malaria endemcities.

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Immunodiagnostic assays for thyroid and other hormonal disorders, including diabetes, were also developed. A dot enzyme immunoassay for simultaneous measurements of autoantibodies against thyroglobulin and thyroid microsomes, which does not require any sophisticated equipment, was developed. This was complemented later with an ELISA for thyroid autoantibodies. At the same time, a sensitive ELISA for thyroid stimulating hormone (TSH) useful for diagnostic and epidemiological studies was also developed. Highly sensitive radioimmunoassays for various steroid hormones were also developed and used locally. A cortisol assay which measures salivary cortisol and therefore approximates free cortisol levels was a useful development. Non-isotopic ELISA were also developed for pituitary peptide hormones using polyclonal and monoclonal antibodies, as an alternative to RIAs and IRMAs for these peptides. Assays were also developed to overcome problems of transport of specimens such as blood or sera. A glycosylated haemoglobin measurement by filter paper microcolorimetric method was the first to be tried and further refined. With these methods of sample collection and storage, epidemiological studies in difficult terrain could be achieved.

The necessity to produce diagnostic reagents of defined specificity and sensitivity cannot be overemphasised. Some reagents are easily available through in vivo replication in animal models or in vitro culture of the disease agent. Others are difficult to produce using these conventional techniques and in these instances, recombinant DNA techniques for the production of DNA probes, or where appropriate, production of fusion proteins or oligopeptides using the pin technology of Geysen is applicable. The latter allows the production not only of defined oligopeptides but also minotopes that can mimic antigenic epitopes of disease agents recognised by the immune system.

The future emphasis will be the application of newer tools like the PCR amplification of nucleic acid for increased sensitivity in diagnosis. Examples of the potential use of this technique in infectious diseases will be in the rapid diagnosis and serotyping of dengue infections. Another example will be its use in confirming infection with RI resistant strains of Plasmodium falciparum parasites to antimalarials, where a negative result on microscopy at the first post-treatment week, may actually be false and parasites may in fact be detectable after amplification of parasite DNA. In this connection DNA probes for P. falciparum are already available and with the development of more sensitive non-radioisotope labelling techniques, the practical use of such nucleic acid probes in many clinical laboratories is a distinct possibility.

Another area of intense research in the next couple of years will be the production of recombinant proteins such as diagnostic reagents. Currently this is being carried out for Japanese B encephalitis, dengue, toxocariasis, toxoplasmosis, malaria, filariasis and other infectious diseases in a number of laboratories. Some of these have been produced and are currently being tested for use in diagnosis. With the complementary use of MABs, more specific diagnostic assays to detect antigens and antibodies will be available not only for diagnosis at the patient level but also for seroepidemiological studies to evaluate disease endemicity and the effectiveness of control programmes.

The emphasis on the development of diagnostic assays for the above disease needs no apology, for it addresses the direct needs of the Ministry of Health in the provision of health care to the population. Research funding from the Ministry of Science, Technology and Environment, Malaysia, through the Intensification in Priority Areas (IRPA) mechanism, was extremely generous during the last few years and was directly or indirectly responsible for the successful development of a range of diagnostic tests which are currently being utilised for patient management and control programme purposes. Although continued funding for such research will be vital, researchers in Malaysia must utilise fully the potential power of the new tools of molecular biology for medical research. In particular, more medically qualified personnel must be trained in these areas and encouraged to carry out such research.
References


