PROFESSORIAL LECTURE SERIES

MOLECULAR CELL BIOLOGY, BIODIVERSITY AND BIOTECHNOLOGY

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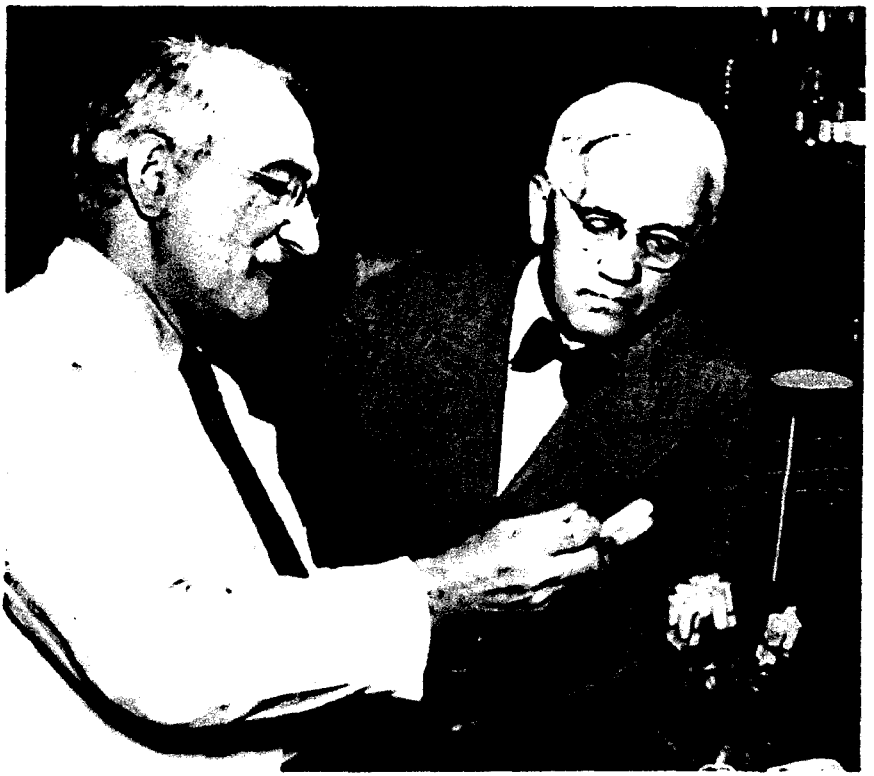

Plate 1: Dr. Selman A. Wakesman (left) and Sir Alexander Fleming (right), both scientists won the Nobel Prize in Medicine or Physiology, were discussing the microbes which produce medically important antibiotics.
(Courtesy of American Society for Microbiology)

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PREFACE

This book is based on the text of my professorial lecture delivered at Universiti Malaysia Sabah, Kota Kinabalu in 2003.

I have chosen the title *Molecular Cell Biology, Biodiversity and Biotechnology* in view of the decision and commitment of the Malaysian government to develop the biotechnological industries. One such effort is the development of the future Biovalley, near Kuala Lumpur.

Malaysia's hopes to utilize the rich biodiversity of the tropical rainforests as one of the competitive factor. While much of the emphasis have been based on traditional indigenous medicinal plants, I point out in my lecture the importance of focusing on the rich microbial diversity, the filamentous bacteria , actinomycetes; myxobacteria and fungi, which have produced most of the important antibiotics and other pharmaceutical compounds. In fact, success in exploiting the rich microbial diversity for biotechnology is highly dependent on our deep understanding of the molecular cell biology of the normal and pathological cell.

I have chosen to discuss current research work in my laboratory at Universiti Malaysia Sabah on the screening of microbial inhibitors for tuberculosis, cancer and Alzheimer's disease (memory loss). It is very significant that most of the key molecular targets are protein kinases and phosphatases involved in signal transduction and cell cycle of bacteria and eukaryotes (yeast to man).

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I am also indebted to my father, Hoe Leong Kim; my mother Chong Yang and my family, Doris Yap Geok Khim, Paul Ho Pow Leong, Christina Lye and Bernice Ho Yin Mae for love and support. This lecture is dedicated to the memory of my late wife, Florence Chin Siew Yin.

ABSTRACT

This lecture concerns the interaction between the rich biodiversity of Malaysia, particularly that in Sabah and the current major discoveries in molecular cell biology, related to both normal cell functions such as cell division and the abnormal functions of the pathological cell leading to infectious diseases, such as tuberculosis, and non-infectious diseases, such as cancer and Alzheimer's disease. The biodiversity includes animals, plants and the invisible microbes like the filamentous bacteria, actinomycetes, myxobacteria and fungi. These microbes are prolific producers of diverse type of bioactive secondary metabolites acting as antibiotics and non-antibiotic activities. The advanced molecular cell biology of the pathogen (i.e., *Mycobacterium tuberculosis*) and the human cell including the sequence of bases for all the genes in their genomes have identified many molecular targets (i.e., proteins) for these secondary metabolites. This will certainly led to the discovery of novel biochemical reagents and further the understanding of the cell. It will also lead to new drug discovery for diseases with inadequate treatments, such as cancer, and those with no effective drugs, such as memory loss in Alzheimer's disease. These natural product pharmaceuticals complement other routes of drug discovery by chemical syntheses using (1) conventional, combinatorial chemistry, computer aided drug design or (2) human recombinant therapeutic proteins or vaccines created through genetic engineering.

The potential of drug discovery utilizing the Malaysian rich microbial resources are illustrated by three studies carried out in our laboratory at Universiti Malaysia Sabah and assisted by several undergraduate and postgraduate students. These studies are summarized as follows:

Tuberculosis

Tuberculosis, a reemergent serious infectious disease world wide, is especially serious in poverty-stricken Asian and African countries. The problems of multi-drugs resistance, coupled with reactivation of latent and persistent infection afflicting HIV patients, demand the discovery of new TB drugs. In view of these problems, we have screened extracts of actinomycetes and fungi from Sabah against isocitrate lyase, an enzyme produced in the glyoxylate pathway when the mycobacteria switched to fatty acid utilization during latent infection. As a result, one potential inhibitor similar to itaconic acid has been discovered and characterized.

Cancer

The molecular understanding of the causation of cancer as genetic defects of the somatic cell leading to uncontrollable cell proliferation has indicated that many of the cancer genes (i.e., oncogenes and tumor suppressor genes) involve protein kinases and phosphatases through phosphorylation and dephosphorylation in signal transduction and cell cycle. Thus, protein kinases are now key targets in the discovery of inhibitors for cancer treatment. Recently a synthetic oral drug Gleevec has been approved for treatment of chronic myeloid leukemia, for it has been found that the drug acts by inhibiting the tyrosine kinase of the translocated Bcr-Abl Philadelphia chromosome. With regard to this, we discovered that an inhibitor interrupting the Ras-raf protein interaction in the mitogen activated protein (MAP) kinase pathway, with consequent decreased phosphorylation of the downstream MEK1/2 and ERK1/2 kinases.

Memory Loss and Alzheimer's Disease

Signaling for neurological functions for example memory in the brain, also acts through protein kinases and phosphatases especially at the synapses between neurons. Recently it was discovered that the serine-threonine protein phosphatase I (PP1) is a constraint to learning and memory.

In our laboratory, we have succeeded to find a potential inhibitor of the catalytic site (Glc7) of PP1 in yeast. This inhibitor will be purified and tested for memory remediation. The severe loss of memory in Alzheimer's disease resulted from neuronal death related to extracellar beta-amyloid plaques and intracellular tau tangles. These tau tangles are hyperphosphorylated by cyclin dependent kinase 5 and GSK-3β. We also intend to screen for inhibitors against these kinases.

In the development of biotechnology based on biodiversity, it is imperative to adopt an integrated approach to conserving biodiversity (both *ex-situ* and *in-situ*) involving bioprospecting, biotechnology and commercialization.