Research at IMU: achievements, thrust areas and future challenges

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Abstract: There have been significant achievements in research at IMU as indicated by the increasing amount of external funds obtained, and number of publications and postgraduate students produced since it started its research activities in the year 2000. However, it is a great challenge indeed to ensure sustainability of our research, which is currently heavily dependent on internal funding. There is a need to realign our strategies to further enhance our competitiveness in securing external funding for research. In line with this, the Institute for Research, Development and Innovation (IRDI) was officially established on 18 September 2012. The Institute will serve as a platform to support all research activities at IMU. There are four Centres of Excellence based on the identified thrust areas under IRDI, namely 1) Centre for Bioactive Molecules and Drug Discovery; 2) Centre for Environmental and Population Health; 3) Centre for Cancer and Stem Cell Research, and 4) Centre for Health Professional Education Research. Major findings based on research in these four thrust areas are reviewed in this paper. With the strategic planning and establishment of IRDI, it is our aspiration to bring research at IMU to a higher level.

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Introduction

Research is an integral component of education, which forms part of the academic and scholarly activities of an academic institution. The conduct of research will contribute to achieving academic excellence, which is part of the core values of the International Medical University (IMU). Research is part of the framework of scholarship activity, particularly in the pursuit of the scholarship of *discovery*.[1] Pursuing excellence in research is in line with the Mission '*To be a leading private Asian healthcare educator that creates value through integrating education, healthcare and research*' under the ASPIRE strategic plans of IMU.

Since obtaining university status in 2000, IMU has placed great emphasis on developing its research activities. At the initial stage, research was mainly supported by internal grants, as private universities were not entitled to government funding then. Internal grants amounting to RM 41,000 were given in support of the first seven projects in 2000. Since then, the amounts of internal grants have been increasing, reaching RM 1 million per year to support faculty and postgraduate research, with another RM 1.5 million per year for equipment support. There is also additional funding of RM 900,000 to support undergraduate research, as required under the various programmes in Medicine (BMedSci), Dentistry, Pharmacy, Medical Biotechnology, Biomedical Science, Nutrition and Dietetics, Pharmaceutical Chemistry, Psychology and Nursing.

A credible environment and infrastructure has been established to support research activities at IMU. Within the last five years, the floor space for research has doubled to more than 26,000 square feet. The IMU Research Laboratory (IMU-RL) is equipped with facilities for studies on genes, gene products and biomarkers, recombinant molecules, bioactive molecules, drug delivery, cancer and stem cells. There is also an animal holding facility with expanded space (about 770 square feet) and state-of-the-art caging and maintenance of experimental animals. An Environmental Health Laboratory equipped with an Inductively Coupled Plasma- Mass Spectrophotometry (ICP-MS) machine was recently set up for the testing of toxicants such as heavy metals in environmental and food samples. The facilities in IMU-RL not only support research but are also important for providing services to the industry.

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Research Outputs

There has been much progress since IMU started its research more than ten years ago, as indicated by the increased number of publications produced, postgraduate students trained and external grants received. The total number of publications from IMU has increased from 123 in 2008 to 212 in 2011, with the increase of total impact factor from 77.97 to 274.03 (Table 1). Our researchers have successfully secured grants from external sources to support their projects (Figure 1). The major sources of external funding were from the Ministry of Higher Education (FRGS and ERGS) and Ministry of Science, Technology and Innovation (E-Science Fund), while substantial amounts of funding also come from research foundations such as Ranjeet Bhagwan Singh Grant, MAKNA Research Grant and Malaysia Toray Science Foundation (MTSF). There were also several collaborative projects with the Malaysian Palm Oil Board (MPOB) on tocotrienols and drug formulation based on palm oil.

In 2011, IMU researchers had successfully secured FRGS and ERGS grants for seven projects, amounting to RM 436,350. In 2012, four young researchers from IMU were awarded a total of RM 85,000 from the MTSF. Strategic collaboration with fellow researchers from local universities and research institutions as well as partner schools has been established for joint application of external funding.

Our researchers have also attracted external grants from international pharmaceutical and nutraceutical companies. There were several multinational clinical trials conducted by IMU researchers sponsored by pharmaceutical companies such as Norvatis, Astra-Zeneca, Benflorex-Servier, and Boehringer-Ingelheim. In addition, there were contract research projects funded by industrial partners such as Bioven and Yakult Honshu. The Bioven project was on the production of immune vaccines while the Yakult project was on probiotics. In terms of human capital training, we have produced a total of 9 PhD and 24 MSc graduates since 2004. In addition, two patent applications were filed in 2011.

Thrust areas of research

The research programme at IMU that was started as an ad hoc programme based on the interest of faculty members has evolved into one which caters to the needs of individual interest, expertise available, external funding opportunities, and potential for consultancies and commercialisation.

Research activities in the early phase were initially in the areas of interest of researchers and were then progressively directed into seven defined areas, namely: 1) Bioactive molecules; 2) Cancer biology and related stem cell research; 3) Pharmaceutics and drug delivery systems; 4) Natural compounds and nutraceuticals; 5) Environmental health research; 6) Clinical research and 7) Medical education research.

Some of the above areas have developed much faster than others. Presently, four thrust areas where IMU researchers can compete to bid for external grants, and contribute substantially in contract research, consultancy, product development, and services have been identified, these being: 1) Environmental and population health; 2) Cancer and stem cell research; 3) Bioactive molecules and drug discovery; 4) Health professional education research. An overview of the findings derived from research activities in these thrust areas are given in the following sections.

Environmental and Population Health

This is an area that has attracted much interest amongst IMU researchers. Studies on airborne organisms such as algae, parasites, fungi, bacteria and dust mites are of particular interest as they have been implicated as agents that may cause 'building-related illnesses' amongst occupants in office buildings (Fig. 2). One study showed that the parasite *Acanthamoeba* was detected in 20 out of 87 dust samples collected from air-conditioners in a building in Kuala Lumpur.[2]

The parasite was isolated and their characteristics were studied based on morphological and molecular features. Results showed that some of the isolates could be potential human pathogens. Besides parasites, dust mites are another group of airborne organisms studied by our researchers.[3] Six species of mites were identified based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) of the ITS-2 gene. Allergens from dust mites could be an aetiological factor that contributes to diseases such as asthma, rhinitis and eczema.

Studies were also conducted on airborne organisms in outdoor environments. For instance, a survey was conducted to document the occurrence of airborne algae within Bukit Jalil in Kuala Lumpur.[4] It was found that cyanobacteria (blue-green algae) were the dominant airborne algae in this township, with a total of eight species identified. Human movement appeared to be an important factor affecting the occurrence of airborne algae. High percentage occurrence of airborne algae was recorded at an animal holding facility house and the Light Railway Transit (LRT) station. In contrast, very low occurrence of airborne algae was recorded at the sites around Tasik Komanwel.

In another interesting study, the parasite *Cryptosporidium* was isolated from the droppings of 37 bird species from the National Zoo in Kuala Lumpur.[5] The isolates of *Cryptosporidium* were identified using molecular techniques based on 18S tRNA gene. Consumption of food contaminated with the parasite is known to cause diarrhoea. The birds may pose a threat to public health as they may act as an agent that spread the parasite.

The use of algae as biological tools to monitor and assess the toxicity of environmental pollutants such as pesticides, heavy metals, pharmaceuticals and hair dyes is another area of research in environmental health. Algae are of particular interest as they form the basis of the food chain in the ecosystem. Any adverse effect on algae may be passed on to the organisms at the higher trophic levels of the food chain, which may ultimately pose a risk to human health. Our studies revealed that pollutants such as pesticides may cause damage to DNA in both algae and animal cells. In addition, the widely used biocide triclosan was found to inhibit growth of freshwater algae such as *Pseudokirchneriella subcapitata* and *Chlorella vulgaris*. Another study showed that acid phosphatase activity decreased in the marine microalgae *Dunaliella tertiolecta* and *Pavlova gyrans* when exposed to high levels of cadmium and copper. Nitrogen and phosphorus, which are the main contaminants that could trigger eutrophication were found to influence the toxicity of heavy metals in the marine microalgae.

There was also interest in the study on toxicity of environmental pollutants using animal models. For instance, exposure of stress and dermal application of low doses of the pesticide chlorpyrifos was shown to have neurotoxic effect in adult mice as indicated by the up-regulation of the expression of glial fibrillary acidic protein (GFAP) in the hippocampus.[6] It was also found that the dermal application of chlorpyrifos caused a more significant decrease in serum acetylcholinesterase in adult compared to young mice.[7] Another study showed that long-term exposure to lead in rats may result in damage to bone marrow due to oxidative stress.[8] There was also interest in the apoptotic effect of the hair dye component para-phenylenefiamine (p-PD) in liver cells.[9] The study found that the apoptotic effect was due to formation of reactive oxygen species (ROS) and activation of p38 and c-Jun N-terminal kinases (JNK) induced by p-PD.

One of the main focus areas in public health research is on human nutrition. Most of the studies aimed to correlate nutrient status with various diseases, and nutrients such as fatty acids, folate and vitamin D are of particular interest. One study aimed to find out the association between dietary fatty acid intake and homocysteine levels in relation to heart disease.[10] It was found that diets high in palmitic acid (16:0), lauric and myristic acid (12:0 + 14:0) or oleic acid (18:1) do not alter postpandrial or fasting plasma homocysteine

and inflammatory markers in healthy Malaysian adults. Another study reported on the folate contents in some commonly consumed vegetables, fruits, legumes and cereals, which ranged from 2 – 156 μg/100 g dry weight, and concluded that some of the underutilised vegetables and fruits are good sources of folate.[11]

A study was conducted to find out the prevalence of vitamin D insufficiency and its association with Body Mass Index (BMI) amongst primary school children in Kuala Lumpur[12] while another study was performed to determine the cut-off values of BMI in Malaysian population for the detection of the risk factors for diabetes mellitus, hypertension and hypercholesterolaemia.[13] The findings indicated that BMI cut-offs of 23.0 kg/m^2 in men and 24.0 kg/m^2 in women are appropriate for classification of overweight in the Malaysian population. The impact of micronutrient interventions on cognitive performance of children aged between 5 and 15 years in the developing world was reviewed.[14] In relation to population health, a study on maternal, neonatal and child health in Southeast Asia identified three major patterns of maternal and child mortality reductions, and suggested that increased policy support is needed to achieve health goals of these three population groups.[15]

Other areas of public health research included reproductive health,[16] respiratory disease,[17] and complementary and alternative medicine.[18] There was also interest in infectious diseases such as leptospirosis[19] and candidiasis.[20] Another study focused on the onset of chronic infection of *Toxoplasma gondii* and reactivation of brain cysts in a mouse model.[21] In addition, a meta-analysis was conducted to investigate the association between hepatitis C infection and malaria.[22] There was also a study assessing the prognostic utility of rheumatoid factor isotypes and anticyclic citrullinated peptides in rheumatoid arthritis patients.[23] The pathogenesis of the skin disease psoriasis is another area of interest. Comparative immunohistochemistry study revealed that the expression of vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) increased in skin samples from psoriatic patients.[24]

Bioactive molecules and drug discovery

Research in this area focuses mainly on the extraction of compounds from a wide range of biological resources including algae and various plant materials. The organisms were screened for various biological activities including antioxidant, anticancer and anti-inflammatory activities. For instance, parasporal proteins from the soil bacterium *Bacillus thuringiensis* were found to induce cell cycle arrest and apoptotic cell death in leukemic cells.[25] Another study found that the snake venom from king cobra contained an antibacterial protein belonging to L-amino acid oxidase.[26]

The bioactive molecules of interest include natural compounds such as tocotrienol, astaxanthin, zingerone, apigenin, carrageenan and phycocyanin.[27] There were also studies on the production of monoclonal antibodies against *Candida albicans*. There was keen interest in research on palm tocotrienols, which are known to have various health-promoting benefits and potential therapeutic applications.[28] In addition, screening of extracts from various organisms for biological activities were conducted. For instance, extracts from microalgae were found to have inhibitory activities against Epstein Barr virus (EBV) in lymphoblastoid cells.[29] There was also a report on the screening of standardised methanol extracts from medicinal plants including *Momordica charantia* and *Andrographis paniculata* for antiviral activities against the dengue virus.[30] Ethanol extracts from the plants *Strobilanthes crispus* and *Pandanus amryllifolius* were found to have apoptotic effect against breast cancer cell lines.[31,32] There were also several studies on antioxidant activities of extracts from various organisms. For instance, methanol extract from *Spirulina platensis* was found to have protective effect against cell death induced by oxidative stress.[33] Another study showed that methanol extract from the plant *Solanum jasminoides* has strong free radical scavenging activity based on chemical assays.[34]

In relation to drug delivery, a study found that co-administration of spiramycin with metronidazole was

effective in reducing *Toxoplasma gondii* brain cysts in a mouse model.[35] A recent review discusses the development and potential applications of technologies in buccal and sublingual drug delivery systems.[36] There was also interest amongst our researchers in drug formulation studies. For instance, solid dispersions of nitrendipine were found to have higher solubility compared to the pure drug.[37] In addition, there was a study on the characterisation and *in vitro* drug release of a formulation based on polysaccharide from *Terminalia catappa*.[38]

Cancer and stem cell research

Various aspects of cancer research ranging from causes and mechanisms, detection and diagnosis to prevention and treatment of cancer were investigated by IMU researchers. For instance, a study found that tumour growth factor (TGF)-β upregulates the expression of survivin which leads to the resistance to apoptosis in nasopharyngeal carcinoma cells.[39] The use of nanotechnology in drug delivery is a recent development in cancer treatment. In relation to this, it was found that multidrug resistance in breast cancer cells could be reversed by silencing ATP-binding cassette (ABC) transporter genes with nanoparticle-facilitated delivery of target siRNAs.[40] Another study reported that suppression of the B cell lymphoma-2 (BCL-2) gene could enhance the sensitivity of nasopharyngeal carcinoma (NPC) cells to cisplastin.[41] There was also a meta-analysis on the effectiveness of the use of buprenorphine for treating cancer pain.[42] An exploratory study was conducted in Tuanku Jaafar Hospital, Negeri Sembilan, Malaysia to assess the effect of chemotherapy on cognitive function of patients with breast and cancer colon cancers.[43]

The anticancer effect of various nutraceuticals is another area of interest. For instance, palm tocotrienols were found to decrease the levels of pro-angiogenic markers in human umbilical vein endothelial cells (HUVEC) and murine mammary cells.[44] Another study found that delta- and gamma-tocotrienols could induce apoptotic changes in human T-lymphoblastic leukaemic cells.[45]

There were several case reports on cancer published by clinicians from IMU. For instance, there was a case report on follicular carcinoma of the thyroid which presented as distant metastases.[46] Another case report was on the presence of cutaneous metastases in squamous cell carcinoma of the head and neck.[47] In addition, there was a case report on the unusual cause of neuropathy due to the extensive dural spread of primary cervical osteosarcoma.[48]

In relation to stem cell research, the potential therapeutic applications of human mesenchymal stems cells (hMSC) are one of the major areas of interest at IMU. For instance, in a clinical study, bone marrow mesenchymal stromal cells were transplanted to patients with end-stage ischaemic heart failure.[49] The study found that there was significant improvement in cardiac function and volume, resolution of scarring and increased wall thickness for all patients six months after treatment. In another study, hMSC were transfected with a plasmid vector expressing human cytokine interleukin-12 (IL-12), and the results showed that the transfected stem cells retained their immunophenotypes and the differentiation potential into adipocytes and osteocytes.[50] The results indicate that hMSC may be a suitable vehicle for gene therapy. While the potential applications of hMSC are being explored, the harmful effects of such cells, especially their tumorigenic potential should be further assessed, as highlighted in a review by Wong *et al.* (2001).[51]

Health Professional Education Research

In the early years, research on professional education focused mainly on medical education, with major interest in areas such as problem-based learning (PBL), assessment and evaluation, curriculum development, ethics and professionalism and clinical training. With the introduction of other health science programmes, the research areas were expanded beyond

Medicine to cover other health professions such as Dentistry, Pharmacy and Nursing. A compilation of abstracts of papers and presentations in Medical Education of IMU researchers from 2000 to 2011 was published in conjunction with the 20th Anniversary of IMU.[52]

Amongst the health professional education research, one study assessed the undergraduate competence in evidence-based medicine using two validated instruments, namely the Fresno test and Berlin Questionnaire.[53] Another study evaluated the usefulness of debate as a tool in teaching health economics to dental students.[54] There were also studies on the effectiveness of assessments and evaluation in the various academic programmes, including in-course assessment in Pharmacy,[55] written tests in Nursing[56] and OSCE in Medicine.[57] In addition, a qualitative study was conducted to analyse the learning experience of students through literature in medicine.[58]

Key Challenges

One of the greatest challenges faced by IMU is the heavy dependence of internal grants to support research, especially in the postgraduate and faculty research projects, which amount to RM 1.5 million per year. One strategy to ensure the sustainability of research at IMU is that efforts should be invested to enhance the competitiveness of our researchers in securing external funding through government funding (MOHE and MOSTI), international grants (e.g. Welcome Trust and Bill and Melinda Gates), and contract research (e.g. pharmaceutical companies). There should be more strategic partnerships with other institutions in the country and abroad to tap the external funding available.

There is also a need to realign our research activities towards the thrust areas that have been identified, which may need to be aligned with funding opportunities (e.g. nanotechnology) and national priority areas. There should be more emphasis on the recruitment of new faculty with the relevant expertise in research as faculty with good track record will have better chance in securing grants. In addition, the research and working environment should be conducive to retain good researchers.

Postgraduate students are one of the most important factors that contribute the progress of our research. Human capital development as measured by the number of postgraduates produced is one major output from any research grants. Thus, it is crucial that IMU continues to attract students to register for its postgraduate programmes. It is important to maintain the high quality of the postgraduate programmes, and to ensure that there are well-qualified and experienced supervisors.

A strategic move to enhance our research is to tie up with an appropriate industry (e.g. edible bird's nest and herbal products) by providing testing services for their products. For instance, while the industry may have extraction facilities for herbal products, IMU could provide *in vitro* and *in vivo* testing services to assess their biological activities. Such linkages will not only generate revenue through commercialisation of our research services, but also offer opportunities for training of undergraduate and postgraduate students.

Another major challenge is the impact of economic slowdown and change in government funding policies. It has been a great challenge indeed to compete with so many public and private institutions for the limited funding from government sources. The strategy adopted by IMU to tackle this challenge is by identifying thrust areas which are broad-based rather than being too specific, which allows us to fit into different priority areas.

Establishment of IRDI

The Institute for Research, Development and Innovation (IRDI) was established as part of the strategic plans of IMU to realign its research activities in attempts to tackle the challenges mentioned above. The IRDI was officially launched by the Chancellor of IMU, Dato' Sri Dr T Devaraj on 18 September 2012.

The primary aim of IRDI is to serve as a platform to support all research activities at IMU. The objectives of IRDI include the following: 1) To explore funding opportunities; 2) To liaise with industrial partners for contract research; 3) To provide supporting services to researchers such as statistical and editing services, and advice on IP filing; 4) To coordinate the applications for both internal and external funding; 5) To coordinate the commercialisation of potential research products and services; 6) To coordinate corporate communication to publicise IMU research.

The IRDI is headed by a Director who reports directly to the Vice-President, Research (Fig. 3). The Director oversees the strategies and functionality of the Institute, and provides leadership to the scientific community of the university. The Research and Ethics Joint Committee is an important component of the Institute, playing a key role in evaluating research proposals for internal and external funding. In addition, there is a Scientific Advisory Board, consisting of distinguished scientists in the leading fields as well as representatives from the industry to advise on the research direction of the Institute, aligned with its strategies.

There are two main arms under IRDI, namely the Research and Development Arm, and Commercialisation and Support Arm. The main functions of the Research and Development Arm are as follows: 1) To drive research activities under the identified thrust areas; 2) To manage the resources for research; 3) To monitor and evaluate all research activities, including those conducted by undergraduate and postgraduate students.

Under the Research and Development Arm, there are four Centres of Excellence (CoE) based on the identified thrust areas:

1. Centre for Bioactive Molecules and Drug Discovery
   The research areas include but are not limited to isolation of bioactive molecules, chemical synthesis and lead identification, screening for bioactivity, preclinical drug development, drug delivery systems and mechanisms of action of drugs.
2. Centre for Environment and Population Health
   The research areas cover various aspects of environmental and population health, which include water and air pollution, building-related illnesses, toxicology, and infectious and non-infectious diseases.
3. Centre for Cancer and Stem Cell Research
   The focus areas of this centre include fundamental cancer biology, molecular cell signaling, cell-based therapy, stem cell biology, biomarkers and drug target discovery.
4. Centre for Health Professional Education Research
   This centre will spearhead research related to health professional education (Medicine, Pharmacy, Dentistry and Health Sciences). The thrust areas include problem-based learning (PBL), inter-professional learning, peer teaching, teaching excellence and scholarship, e-learning and workplace-based learning.

The Commercialisation and Support Arm consists of two major units, namely the Commercialisation and Business Development Unit, and Support Unit (Fig. 2). The main functions of this Arm are as follows: 1) To coordinate the commercialisation of potential research products, findings and services; 2) To recommend and provide advice on patenting of research findings, products and processes; 3) To liaise with potential industrial partners for contract research; 4) To facilitate corporate communication for research with the aim of publicising IMU's research to attract more funding; 5) To provide supporting services such as statistical advice, utilisation of bioinformatics tools, editing services for publications and grantmanship training; 6) To ensure efficient utilisation and proper maintenance of all research facilities and equipment; 7) To enhance the quality of research through QC, QA and audit (e.g. ISO), and training (e.g. Good Clinical Practice Seminar) and 8) To enhance research culture within IMU.

As part of the commercialisation activities, IRDI is exploring the opportunities for industrial linkages which over time, could evolve into a research park. The idea is to link up with industrial partners to create research hubs within the different industries and current technology parks in the countries. Through such strategic linkages, it is hoped that intellectual capital and R & D products could be translated to commercialisable applications as well as assist in the development of industrial products.

Concluding remarks

Although IMU is a relatively 'young' university, there have been significant achievements in its research based on the outputs in terms of publications and external grants secured. However, there should be more concerted efforts to drive research to a higher level. The realignment of its research strategies through the establishment of IRDI is in line with this aspiration. Efforts should be invested to enhance the capability of our researchers through various training workshops. As IMU is now part of the IHH Group, which owns a consortium of hospitals, it is high time that we tap on the opportunity to strengthen our clinical research and to provide bioequivalence studies. In terms of commercialisation potential, there is a need to consolidate our business strategies under the Commercialisation and Support Arm.

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Table 1: Research output in terms of number of ISI publications from IMU.

Year	Publications		Total Impact Factor	Mean Impact Factor
	ISI Journals (%)	Total		
2008	37 (30.1%)	123	77.97	2.108
2009	47 (41.6%)	113	120.24	2.558
2010	81 (55.5%)	146	206.01	2.543
2011	116 (54.7%)	212	274.03	2.362

Figure 1: Total amounts of internal and external grants secured by IMU from 2000 to 2011.

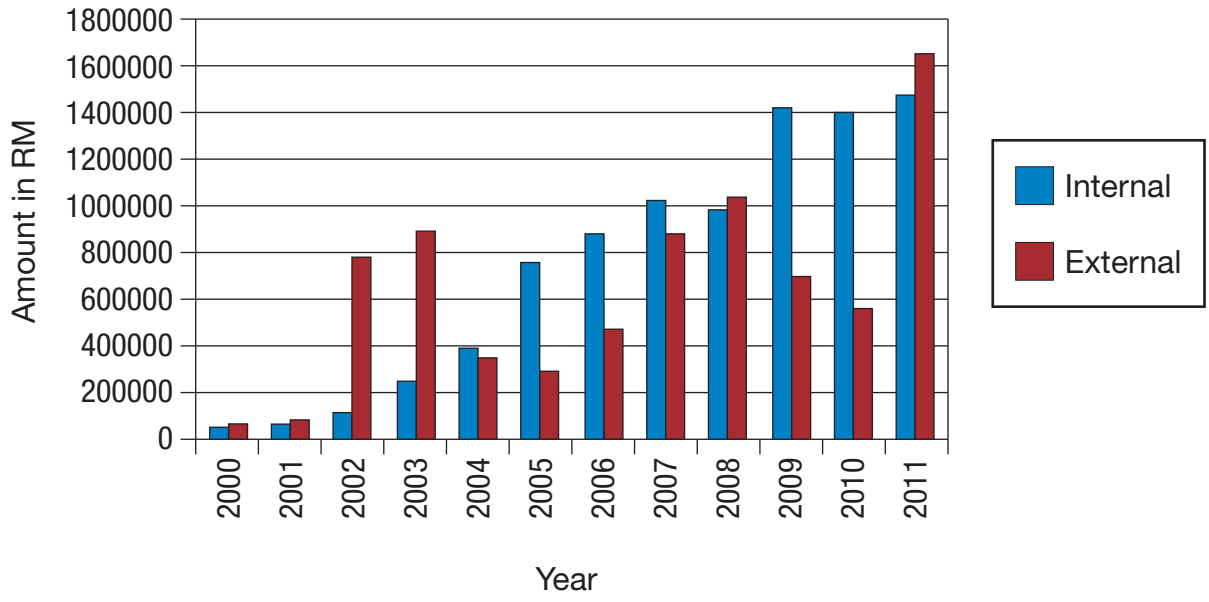

Figure 2: Organisms from indoor environment of an office building in Kuala Lumpur. (a)-(b) *Acanthamoeba* isolated from air-conditioners (Photos courtesy of Dr Chan Li Li); (c)-(d) cyanobacteria; (e) – (f) Dust mites (Photos courtesy of Dr Wong Shew Fung).

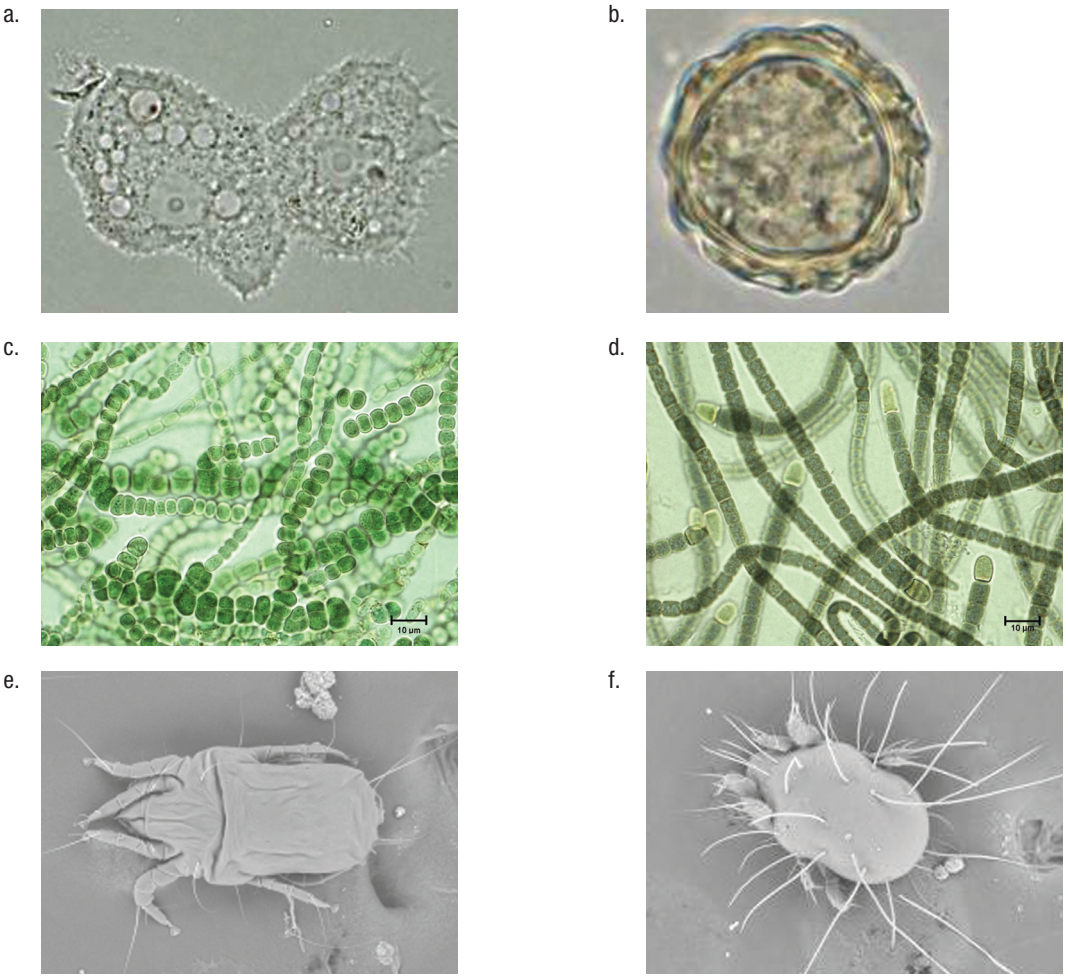

Figure 3: Organisational structure of the Institute for Research, Development and Innovation (IRDI), IMU.