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POSTGRADUATE STUDIES IN MOLECULAR MEDICINE IN MALAYSIA: CHALLENGES AND FUTURE PERSPECTIVE

(Pengajian Pascasiswazah dalam Perubatan Molekul di Malaysia: Cabaran dan Perspektif Masa Depan)

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ABSTRACT

Molecular Medicine consists of a broad range of fields involving physical, chemical, biological and bioinformatics to identify the fundamental issues in medicine. This includes understanding diseases at the molecular level and developing strategic interventions and treatment via personalized and precision medicine. In Malaysia, private and public universities offer a postgraduate Molecular Medicine program. Universiti Kebangsaan Malaysia offers this program through the Faculty of Medicine and UKM Medical Molecular Biology Institute (UMBI) via various research projects involving non-communicable diseases (cancer and non-cancer) and infectious diseases. Several challenges will be discussed, including limited research funding and competitive grant applications, particularly international grants. Research funding is necessary, impacting the quality of postgraduate research. Second, the infrastructure and access to the needed reagents could be improved since most companies providing these services are from the USA, European countries and the United Kingdom. In addition, the instruments are expensive, and the technology evolved too fast. Third, an innovative partnership between academia and industries must be enhanced to support the research ecosystem better. The biotechnology companies may also provide a

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place for attachment for the students to experience the working culture in industries, apart from their formal education in the university. Pursuing postgraduate studies in Molecular Medicine still offers a valuable experience for students, even with these significant obstacles. These challenges can be overcome via several strategies, which will be discussed in the article.

Keywords: Postgraduate studies; Molecular Medicine; Challenges and Future Perspective

ABSTRAK

Perubatan Molekul terdiri daripada pelbagai bidang yang melibatkan fizikal, kimia, biologi dan bioinformatik untuk mengenal pasti isu asas dalam perubatan. Ini termasuklah memahami penyakit di peringkat molekul dan membangunkan kaedah strategik bagi merawat pesakit melalui perubatan yang diperibadikan. Di Malaysia, pelbagai universiti swasta dan awam menawarkan program Perubatan Molekul di peringkat pascasiswazah. Universiti Kebangsaan Malaysia menawarkan program ini melalui Fakulti Perubatan dan Institut Biologi Molekul Perubatan UKM (UMBI) melalui pelbagai projek penyelidikan yang melibatkan penyakit tidak berjangkit (kanser dan bukan kanser) dan penyakit berjangkit. Beberapa cabaran akan dibincangkan, termasuklah pembiayaan penyelidikan yang terhad dan permohonan geran yang kompetitif, terutamanya geran antarabangsa. Pembiayaan penyelidikan adalah perlu, yang akan memberi kesan kepada kualiti penyelidikan pascasiswazah itu sendiri. Kedua, infrastruktur dan akses kepada reagen yang diperlukan boleh dipertingkatkan kerana kebanyakan syarikat yang menyediakan perkhidmatan ini adalah dari Amerika Syarikat, negara Eropah dan United Kingdom. Di samping itu, instrumen yang mahal, dan teknologi bidang ini berkembang dengan begitu pesat. Ketiga, perkongsian inovatif antara akademia dan industri mesti dipertingkatkan untuk menyokong ekosistem penyelidikan dengan lebih baik. Syarikat bioteknologi juga boleh menyediakan tempat untuk para pelajar merasai budaya kerja di industri, selain daripada pendidikan formal di universiti. Sebagai kesimpulan. melanjutkan pengajian di peringkat pascasiswazah dalam Perubatan Molekul masih menawarkan pengalaman berharga untuk pelajar, walaupun dengan cabaran yang bakal dihadapi. Cabaran ini boleh diatasi melalui beberapa strategi, yang akan dibincangkan dalam artikel ini.

Kata kunci: *Pengajian pascasiswazah; Perubatan Molekul; Cabaran dan Perspektif Masa Depan*

INTRODUCTION

In Malaysia, numerous universities offer a postgraduate program in Molecular Medicine, including public and private universities. These include the University of Malaya (UM), Universiti Kebangsaan Malaysia (UKM), Universiti Sains Malaysia (USM), University Putra Malaysia (UPM), Universiti Teknologi Malaysia (UTM), Monash University of Malaysia and Sunway University. Universiti Kebangsaan Malaysia offers this program through the Faculty of Medicine, Faculty of Health Sciences, Faculty of Pharmacy, Faculty of Dentistry and UKM Medical Molecular Biology Institute (UMBI) via various research projects involving non-communicable diseases (cancer and non-cancer) and infectious diseases.

Based on the National Library of Medicine (NIH, NCBI), Molecular Medicine is a field that applies multi-omics platforms, for example, genomics, transcriptomics, proteomics and metabolomics, to study diseases at molecular levels (National Library of Medicine 2003). The aim is for disease prevention, early diagnosis and determination of the disease prognosis. Understanding diseases at the molecular level could lead to the development of strategic interventions and treatment via personalized and precision medicine. The application of molecular medicine includes gene therapy, genetic epidemiology, molecular and clinical pharmacology, and molecular structural analysis (National Library of Medicine 2003). In Malaysia, private and public universities offer a postgraduate Molecular Medicine program.

The Ministry of Higher Education Malaysia (MOHE) aims to produce 60,000 doctorate holders by 2023, but as of 2016, when this study was conducted, there were only 23,000 doctorate holders in Malaysia (Fong 2016). The MOHE aims to produce 60,000 PhD holders in 2023 to meet the nation's needs for research development and innovation (Fong 2016). Based on a tracer study of postgraduates in Malaysia, reported in 2022, 25,014 PhD candidates have completed their studies from 2011-2022 (PhD holders in natural sciences and maths record lowest employment in 2022 and2023). In 2022 alone, 2,872 PhD candidates graduated in Malaysia (PhD holders in natural sciences and maths record the lowest employment in 2022 and 2023). To help achieve this mission, the top public university in Malaysia welcomed students with relevant qualifications to pursue postgraduate studies in various fields. However, only some students who enrolled in postgraduate studies graduated on time. Using the fuzzy Delphi technique, this study aims to identify the challenges faced by postgraduate students from one faculty at a top Malaysian public university in completing their studies on time. The study found that postgraduate students faced challenges in supervision and research work. At the early stage of the thesis completion, the primary

challenge was selecting the research topic, while at the later stage, the roles of the supervisor became much more prominent. These challenges could be used to improve and contribute to our growing understanding of timely completion as a complex system.

The field of Molecular Medicine evolved fast. Thus, the postgraduate program in this field must be conducted to meet the stakeholders' standards, such as those of academia and industry. The main stakeholders in the Molecular Medicine field are the industry, which includes the technology developers and drug companies who could develop novel drugs for certain diseases. This poses several challenges and issues that need to be addressed in detail. The students need to be adequately trained in-house about the techniques involved in the study. Outsourcing, even though most of the time is cheaper than in-house, has drawbacks, such as students need to learn the method sufficiently. Thus, they need more time to be ready for the industry. A smart partnership with the company should be prioritized, and the student can be attached to the company for a specific time to gain experience in the industry world. Pharmacological companies may be necessary for those students working on drug delivery and target or drug repurposing. However, for postgraduate students in Molecular Medicine, the vital stakeholder is the industry, and the postgraduate program should be tailored to the needs of the industry.

POSTGRADUATE STUDIES IN MOLECULAR MEDICINE IN MALAYSIA: CHALLENGES

MOLECULAR MEDICINE IS A RAPIDLY EVOLVING FIELD

As described earlier, Molecular Medicine involves a broad range of omics studies, such as genomics, transcriptomics, proteomics and metabolomics, to identify the cause of diseases for early detection and treatment. This will also assist the clinician in performing precision and personalized medicine for the patient. Thus, the most suitable medication can be given to the patients, hence reducing the mortality rate due to the disease. Technology in this field emerges frequently and rapidly; hence, keeping up with it is challenging. The instrument, maintenance and reagents are expensive, and maintenance of the instrument needs to be scheduled accordingly. This requires a large budget to ensure good laboratory practices are installed in the institution. The postgraduate program should be designed to comprehensively study diseases based on a single or several omics platforms so that the fundamental issues about the diseases studied can be determined. Inter-disciplinary combined elements such as artificial intelligence (AI), machine learning (ML) and bioinformatics should be considered.

OPPORTUNITIES IN GRANT FUNDING

Depending on the postgraduate program, whether MSc or PhD, research in Molecular Medicine needs to be supported by a research grant. In Malaysia, there are numerous opportunities for grant funding; for example, from the university ministry, the most common for the Molecular Medicine field are the MOHE, Ministry of Science, Technology and Innovation (MOSTI), and industry grants. International grants such as NEWTON and ICGEB can also be applied by a Malaysian, even though they offered more in terms of the grant amount, however, it is very competitive. The challenges with regard to grant opportunities are as follows. First, internal grants from the university are capped at a maximum of RM100,000 or less. This kind of grant is sufficient for an MSc but not a PhD project. The supervisory team needs to ensure that the scope of the MSc is sufficient and that the student learns a few techniques during their study. Even with a small budget, the supervisory team needs to ensure the quality of the MSc students produced. Here are some study designs that suit the needs of a PhD project with the proposed budget. The title of this PhD thesis is "Gene-gene and Gene-environment Interaction in Type II Diabetic with Coronary Heart-Disease Related Death among the Malaysian Cohort Participants". The aim is to identify genetic factors, gene-gene and gene-environment interactions, and the predictive value of the genetic and non-genetic risk models in T2DM with CHD death among TMC participants. The method used in this study is genotyping via microarray technique and comprehensive data analysis to identify the genetic factors, gene-gene, gene environments interaction and risk prediction models. The study design is case-control with a sample size of 849 samples. The cost of DNA isolation is about RM35/ sample, and microarray is at RM300/ sample. Thus, the total amount needed for this project is about RM300,000.00. This poses a significant challenge in the postgraduate program in the field of Molecular Medicine.

TECHNOLOGY EXPERTISE

As Molecular Medicine evolved rapidly, the technology in this field also evolved. For example, the first Human Genome Project was launched in October 1990 using Sanger Sequencing to provide fundamental information on the human blueprint, the DNA (National Human Genome Research Institute 2023). Researchers from the US, UK, France, Germany, Japan and China are involved in this massive project under the Human Genome Sequencing Consortium. The project was completed in 2003, and more than 90% of the human genome has been sequenced (National Human Genome Research Institute 2022). However, due to technology limitations, about 150,000 areas of DNA sequences still need to be discovered (could be due to a highly repetitive sequence, which the Sanger Sequencing, 2022 could not detect) (National

Human Genome Research Institute 2022). The Sanger Sequencing technique is the first-generation sequencing developed to determine the DNA nucleotide sequence of the DNA, including As, Cs, Gs and Ts. Introducing the second and third-generation sequencing techniques produces a more robust and simplified version of DNA sequencing techniques (National Human Genome Research Institute 2022). In addition, a robust data analysis pipeline enables whole genome sequencing to be performed in less than a month. However, advancements in the molecular medicine field require technological expertise in laboratory and data analysis. The omics platform, either single- or multi-discipline, poses significant challenges, particularly with regard to big data analytics and integrated analysis, in understanding the fundamental issues studied in the postgraduate program.

THE PROGRAM ITSELF

The postgraduate program requirements for graduation include several criteria. For a PhD, the students must complete eight credit hours of coursework, two accepted or published manuscripts in WoS journals, prepare their thesis, and get approval from the university's Senate. For an MSc, the students must complete eight credit hours of coursework, one accepted or published manuscript in WoS journals, prepare the thesis, and get approval from the university's Senate. Figure 1 shows the journey of the postgraduate students, particularly for the UKM UMBI. The laboratory work encompasses samples, basic demographic, and clinical data retrieval, followed by a laboratory experiment and data analysis. In some cases, students may learn bioinformatics analysis to enhance their understanding of disease pathways.

FIGURE 1 The postgraduate's journey in UMBI, UKM

BIG DATA ANALYTICS

Advancements in big data and AI have significantly influenced various facets of society, encompassing the economy, politics, science, healthcare and education. In the field of Molecular Medicine, big data analytics involves integrating and analyzing extensive omics data, including genomics (DNA), epigenomics (Epi-DNA), transcriptomics (mRNA), proteomics (protein), metabolomics (metabolite) and interactomics (protein-protein or protein-DNA interaction) to understand the mechanisms of diseases, which often pose challenges in postgraduate studies due to the heterogeneity of data sources and poor hardware infrastructure (Bohr & Memarzadeh 2020; Ristevski & Chen 2018). Modern techniques, such as next-generation sequencing (NGS) and Genome-wide Association Studies (GWAS), have rapidly advanced, generating a vast amount of data to decode human genetics (Kanzi et al. 2020). NGS data offers unprecedented insights, elevating experimental scenarios to new dimensions by enhancing the resolution for real-time observation of biological events linked to specific diseases (Satam et al. 2023). Nevertheless, the size of NGS data, measured in gigabytes per dataset, presents challenges in data processing. NGS can generate raw data sizes up to 250 GB. Establishing standard pipelines for processing samples at higher institutions with sufficient computational resources can streamline workflows and enhance efficiency. Given the above considerations on data processing, an efficient NGS analysis pipeline has to be built upon non-standard hardware (Kulkarni & Frommolt 2017).

Dealing with big data involves challenges such as adequate storage of inaccessible file formats, especially in healthcare, where high-end computing tools and interdisciplinary collaboration are crucial. The collected sensor data can be stored in a cloud with pre-installed software tools, integrating data mining and machine learning functions to convert information into knowledge. This streamlined approach enhances efficiency in acquiring, storing, analyzing, and visualizing healthcare big data. Annotating and presenting complex data is critical for comprehension, as the absence of relevant information can obscure biomedical research progress. Visualization tools by computer graphics designers play a crucial role in displaying the gained knowledge (Dash et al. 2019; Kulkarni & Frommolt 2017). Big data analysis in healthcare faces the challenge of data heterogeneity, making traditional technologies less informative. A platform processing thousands of samples requires a robust IT infrastructure, typically involving a multi-node compute cluster managed by the institution's core facility or IT department (Fan et al. 2014). The domain of high-performance computing (HPC), especially with supercomputers, enables the rapid discovery of numerous novel disease-causing variants. The abundant data generated often necessitates in-depth high-throughput analysis, frequently constrained by computational power and memory-intensive applications.

Additionally, cloud-based storage and computing solutions, like Illumina BaseSpace or Amazon Web Services (AWS), are increasingly popular, following an Infrastructure as a Service (IaaS) model that provides on-demand access to computing resources such as servers, storage, networking and virtualization (Kulkarni & Frommolt 2017). Operating on high-power computing clusters through grid computing or cloud computing, which offers virtualized storage and reliable services, is essential. These platforms serve as data receivers and analyzers and provide web-based visualizations (Dash et al. 2019). Implementing ML and AI on computing clusters requires advanced algorithms, often written in languages like Python or R. Handling biomedical big data demands expertise in biology and IT, making bioinformaticians well-suited.

In Malaysia, institutes like UMBI have established an HPC platform that offers advanced computing support to researchers, students and industry professionals. Powered by the Intel® Xeon Phi™ processor, UMBI-HPC leverages extensive parallelism and vectorization for robust, high-performance computing significant data analyses, such as WGS of pediatric cancer under the Initiative for Precision Medicine in Pediatric Cancer Therapy (IMPACT) project and GWAS involving 5000 Malaysians with Type 2 Diabetes from The Precision Medicine for Diabetic Individuals: A Joint Malaysia-UK Effort (PRIME) research project. Genomic studies have led to an increased volume of biomedical data due to NGS technology's utilization. An estimated 100 million to 2 billion human genomes may be sequenced by 2025 (Bernasconi 2021). Systematic analysis of omics data alongside healthcare analytics may help enhance understanding of individual patient profiles and improve strategies for precision and personalized medicine.

Additionally, genomic experiments such as genotyping and NGS studies, combined with data from electronic medical records (EMRs), demographic, medical records, clinical trials and insurance records, constitute substantial biomedical big data, enabling more profound research into diseases and treatment options. Integrating these diverse sources is crucial for enhancing treatments and patient care (Marques et al. 2024). Despite the complexity of patient genomic data, commercial organizations leverage it for personalized medical decisions, suggesting a potential game-changer in future healthcare (Johnson et al. 2021).

Big data analytics in Molecular Medicine and healthcare are essential to assist clinicians with diagnosing diseases, early treatment and interventions and towards precision and personalized medicine implementation. "One size fits all" is not appropriate anymore in treating patients with diseases. For example, in Familial Hypercholesterolemia (FH), patients with mutations in the PCSK9 genes are better to be treated with PCSK9 inhibitors such as, rather than the usual lipid-lowering drug treatment, such as statin (Tomlinson et al. 2021). Familial Hypercholesterolemia

(FH) is a hereditary lipid disorder with an autosomal dominant or recessive genetic inheritance, depending on the genes involved, including *LDLR, APOB*, *PCSK9*, and *LDLRAP1 (Rogozik et al. 2024)*. The clinical hallmark of FH includes an elevated low-density lipoprotein cholesterol (LDL-C) level, tendon deposition and premature atherosclerosis (Cohen & Stefanutti 2021). The prevalence of FH is 1 in 300 globally and 1 in 100 in Malaysia (Chua et al. 2021). Early detection of FH could reduce cardiovascular risks significantly (Cohen & Stefanutti 2021).

The decision regarding treatment options in FH patients depends on the genetic mutations involved, which can be achieved through the genomics platform via NGS (Medeiros & Bourbon 2023; Satam et al. 2023). Big data analytics in medicine and healthcare includes integration and large amounts of data from several omics platforms, namely genomics, epigenomics, transcriptomics, proteomics, pharmacogenomics, metabolomics, and combines both biomedical as well as data from the patients, such as personal and family history, environmental and omics data. Big data in healthcare and medicine involves large and complex data collection. Hence, they are challenging to analyze and manage using a traditional approach such as SPSS. Data must be analyzed using a new approach, such as ML and AI. All data are helpful and could assist the clinicians to better understand the disease in a person, to ensure a personalized and precise medicine could be introduced, hence reducing the disease mortality. However, the challenge in achieving this is that implementing several omics platforms requires a considerable budget and expertise to integrate the data. An expert bioinformatician is needed to perform this high level of data analysis. In addition, electronic medical records (EMRs) or electronic health records (EHRs) must be fully utilized in Malaysia's public or private hospitals. Integrating the omics data with the clinical/ biochemical/ environmental data is essential in diagnosing and prognosis diseases (Chen et al. 2023).

PLANNING AND TIME MANAGEMENT

Time management is crucial in a postgraduate program, mainly if the students aim to graduate on time (GOT). It involves organizing and planning to manage time to complete different activities or tasks. Postgraduate programs, either MSc or a PhD, particularly in the field of Molecular Medicine, are comprehensive and demanding, consisting of extensive research (single or multiple omics platform), coursework, reports and writing manuscripts or thesis, which require endless time, struggle and determination. Therefore, postgraduate students need to organize and plan their work efficiently. The student may need to learn how to manage their time effectively to complete the tasks given and maintain the work-life balance. Highly effective and high achieving students always work smart and get things done in less time. Protected personal time is also essential for the student to manage their stress levels, which

could lead to a better quality of life and increased productivity in the student. Based on Rachael Hanna, who is currently studying Applied Meteorology and Climatology at the MSc level at the University of Birmingham, several methods can be used to ensure good planning in the postgraduate program (Hanna 2023). Students need to structure their daily lives in two steps. The first is to create a to-do list where the urgent task needs to be done before the others. Students also need to have a daily schedule and should prioritize their work and choose their productive hours. For example, thesis writing could be done early in the morning, and the students could target at least three pages per day and do it consistently. This is important to ensure that the students can complete the postgraduate program within the timeframe given. Students could also practice the Pomodoro technique, where they could separate the tasks and concentrate on completing the tasks, for example, in 45 minutes, and then take a break to relax before continuing another task. The Eisenhower matrix is helpful for students in deciding the urgency of a task over time. The tasks are divided into four quadrants, as in Figure 1. This will assist the students with regard to prioritization and the most difficult tasks. For example, thesis writing can be done routinely every day with proper planning and guidance from the supervisory team.

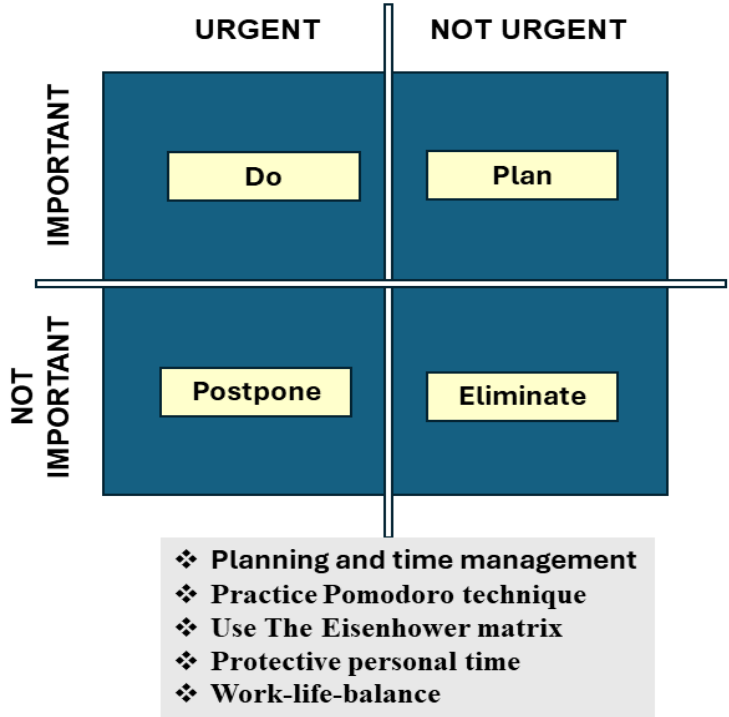

FIGURE 2 The Eisenhower matrix is important which could guide the students on prioritizing the tasks in their postgraduate program (Hanna 2023)

POSTGRADUATE STUDIES IN MOLECULAR MEDICINE IN MALAYSIA: FUTURE PERSPECTIVES

SMART PARTNERSHIP WITH STAKEHOLDERS, THE INDUSTRY AND INTERNATIONAL PARTNERS

In this section, the focus will be on prospects and strategies to overcome the challenges. As discussed in the challenges section, the Molecular Medicine field is expensive and requires a considerable research grant. In addition, with the demand to produce research innovation, a smart partnership with the industry may be a good start for researchers in this field. This smart partnership can be done through various efforts, for example, applying for an industry grant together, co-developing a Single Nucleotide Polymorphisms (SNP) panel of a particular disease, and a student exchange program where the students can be attached to the company to learn the technique. Research collaboration with an international partner could offer a valuable experience for the researchers and the students. International grants offer a sufficient budget to design a quality MSc or PhD project. Once an international grant is received, the smart partnership should be retained, which could lead to a lasting collaborative network between the two parties.

FOCUS ON TRANSLATIONAL RESEARCH RATHER THAN FUNDAMENTAL ISSUES: FROM BENCH SIDE TO BEDSIDE!

Innovation is one of the key performance indices (KPI) in the Malaysian Research Assessment (MyRA2.0) tools for assessing research universities. Fundamental research is essential in understanding the molecular pathways of diseases, but translational research offers more opportunities for researchers to translate the information to the bedside or benefit the patients. For example, in a FH patient, Whole Genome Sequencing (WGS) or Whole Exome Sequencing (WES) could be performed for early diagnosis and family screening in the family members (Vrablik et al. 2020). This approach is essential as FH or hypercholesterolemia is highly associated with cardiovascular diseases (CVD) (Bianconi et al. 2021). FH is usually caused by mutations in the first-tier genes *(LDLR, LDLRAP1, PCSK9 and APOB)*, which could increase the risk of CVD, particularly in patients with homozygous mutations. Homozygous mutant individuals may develop CVD at an early stage of their life (Cohen & Stefanutti 2021). In addition, using WGS or WES, a targeted treatment known as precision and personalized medicine can be implemented where the clinicians could use the genetic information to tailor the best medication for the patient (Pena & Tarazona-Santos 2022). FH patients with PCSK9 gene mutations should be treated with PCSK9 inhibitor instead of statin treatment to lower the total cholesterol (TC) and LDL-C levels in the blood (Tomlinson et al. 2021). By using this strategy, the morbidity and mortality due to CVD could be reduced in the FH patients.

A GOOD SUPPORT SYSTEM

A good support system, the management of the institution and support staff, facilities that include laboratory equipment, and the supervisory team may ease the journey of the postgraduate students. The institution's management must ensure that all students follow the processes and meet graduation needs. The performance of each postgraduate student shall be monitored closely, and any problems need to be tackled early. The support staff of the institution is also essential in guiding the students with technical support for any molecular techniques that the students will use. Administrative staff are equally important to assist the students from registration to graduation. Regarding the facilities, the management must provide preventive maintenance of all equipment used to ensure the results of any laboratory experiments are valid. The management is responsible for providing all the support to ensure that postgraduate students can pursue their studies.

CONCLUSIONS

The postgraduate program in Molecular Medicine has several challenges, including the robust and fast-growing field, which is expensive and requires a tremendous amount of research grants to ensure quality; the program is quite challenging, involving research and coursework. To ensure quality, the MSc and PhD projects need to be designated accordingly with a high standard that could fulfil the needs of the stakeholders, particularly the industry. However, these challenges can be overcome with good support from the institution's management, positive work culture and environment, and the student's determination to complete their postgraduate study. In conclusion, even though complex and challenging, the postgraduate program in Molecular Medicine offers a valuable experience for students.

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