The Institute of Molecular Medicine

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When thinking of premier centres of medical research, investigators from countries such as the United States of America and United Kingdom spring to mind. However, one might forget that there is a centre of research excellence close to home. The Institute of Molecular Medicine (IMM), a venture initiated by Trinity College in partnership with University College Dublin and the Royal College of Surgeons in Ireland, is the premier research facility for molecular medicine in Ireland and has gained a worldwide reputation as a leader in molecular medicine research.

The IMM has the advantage of housing almost 40 top molecular medicine researchers, with specialized fields of interest, but they also work collaboratively to solve complex interdisciplinary problems. Since its opening in 2003, the IMM has focused much of its efforts on cancer, immunology, neuroscience and genomics. The researchers have all published studies in high impact journals such as Nature and Science. Much of the IMM's success is working towards the understanding of genomics and their cellular significance, and translating that information to clinical practice. In this article, four principle investigators are featured to highlight how Trinity College is spearheading research for the advancement of medicine.

The traditional approach of molecular medicine was based on the idea of an underlying genetic abnormality that interacts with the environment to cause disease. Although this basic premise is largely true, according to Dr. Ross McManus, recent research in the genomics of inflammatory disease reveals that normal genetic variants in certain combinations may cause susceptibility to disease. Prof. Michael Gill supports this argument, stating that neuropsychiatric disorders have complex genetic signatures that include genes that were previously thought to be unrelated to the disorder. Thus, elucidation of a patient's genome may allow clinicians to correctly diagnose and individually tailor a therapeutic regime. At first glance, decoding the genome of patients sounds labour intensive and costly. Indeed, Prof. Padraic Fallon predicts that genetic profiles will be useful in the next 5-10 years, but may not be feasible due to cost. Consider the human genome project, which decoded the first genome for the astronomical sum of 2.7 billion US dollars. However, genome sequencing is now possible for only 10,000 US dollars through automated machines. Should this trend to cheaper and faster genome sequencing continue, we might find the use of genetic profiling as a widespread investigation. Prof. Orla Sheils is convinced that the sequencing

will be available for as little as a few hundred Euro, and yield results in hours rather than days.

Medicine will likely change drastically when genomic testing becomes the norm. The mantra for pharmaceutical therapy has always been the use of the "correct drug at the correct dose administered at the correct time." The introduction of widespread genomics will aid in confirming diagnosis, especially those patients with multiple chronic diseases. Correct diagnosis allows the possibility of implementation of a correct treatment regimen. Furthermore, as pharmacokinetics and pharmacodynamics vary widely among patients depending on genotype, phenotype and environment, genomic testing may prove valuable in predicting effectiveness of treatment and tolerability. For instance, essential hypertension is not classified by aetiology and, as such, treatment may include a combination of angiotensin converting enzyme inhibitors, calcium channel blockers, thiazide diuretics, etc. Should a new diagnostic classification system be possible, such as one through genomics, then a more precise diagnosis may be made and targeted pharmaceutical intervention against the most pertinent pathways may be started.

In addition to improving current pharmacological intervention, genetic profiling may provide clues to new pharmaceutical drugs targeting direct genetic expression, suppression, or enhancement in cancer therapy. Pharmaceutical companies have realized that targeted therapy is the future of pharmaceuticals, as haphazard or random drug discovery is immensely expensive and laborious. Although this idea sounds like a pipedream, gene therapy has already seen some early results. Prof. O'Leary and Prof. Sheils' group, in collaboration with the Ear, Nose and Throat clinical teams at St. James's Hospital, have tested a BRAF gene suppressor on a patient with an aggressive form of thyroid carcinoma. The tumour had invaded to the local area, affecting breathing and swallowing and the expected survival was weeks. This gene suppressor counteracts the overexpression of the BRAF gene, which is one of the primary causes of tumourigenesis. After starting the novel treatment a year ago, the tumour shrunk and the patient's quality of life improved.

Indeed, research towards the endpoints labelled here involves more investigators than any single institution can employ. Thus, Trinity College School of Medicine has recently announced that their strategic plan is focused specifically in fields on cancer, immunology, neuroscience, genomics and population health.

Cancer

Prof. Orla Sheils and her group's main focus is the molecular basis of the development and progression of cancer. The group has been involved with elucidation of critical genetic markers in cancer that might aid in diagnosis, prognosis and treatment. Recently, the group was involved in development of molecular diagnosis of cervical abnormalities found during cervical cancer screening. Her group plan to continue uncovering more genetic markers that might be used by clinicians to improve clinical outcomes. Prof. Sheils remarks, "In 20 years, there will likely be effective treatment for many cancers, which will render cancer a chronic disease rather than a lethal one."

Immunology

Dr. Ross McManus and his group investigate genomics of inflammatory diseases, such as coeliac disease and inflammatory bowel disease. In the last several years, his group has assisted in identifying multiple candidate genes, some of which are critical to the pathogenesis to coeliac disease. The future for his group will include exploring the function of genes that are dysfunctional and further differentiating critical genes from trivial ones, allowing the prospect of novel treatments. Dr. McManus believes that in 20 years, there will be effective treatments for coeliac disease and

inflammatory bowel disease, as well as other inflammatory diseases, based on targeted genetic-based therapy.

Prof. Padraic Fallon and his group examine the fundamental mechanisms underlying deranged immune function that lead to diseases such as asthma. To date, his group has provided critical findings that helped unraveled some the processes behind immune function. The future for his group includes further elucidation of mechanisms, so that these processes can be targeted. Prof. Fallon postulates that the future of immunology will improve immensely due to genetic testing, thus enhancing the sensitivity of diagnosis and allowing tailored treatment to be commenced.

Neuroscience

Prof. Michael Gill and his group explore the genomics of neuropsychiatric disorders, such as psychosis and autism spectrum disorders. The group has been involved in multinational research consortiums, where genes have been identified and the functions of some of these genes illuminated. The future of the group focuses on continuing its current course of identifying genes and their functions, as well as creation of cell models that might help demystify the interaction amongst genes and how these genes bring risk. Prof. Gill says, "the future of medicine in neuropsychiatric disorders includes improving diagnosis so that therapies can be applied properly."

Although the next generation of investigations will streamline medicine, a good clinician possesses the basic cornerstones of medicine including examination, communication skills and intuition. As clinicians, we must remember that disease is a complex interplay of pathology, psychology and social circumstance, resulting in diverse presentations of similar medical problems. Medical technologies will aid in differentiating diagnoses and mitigating the effects of disease, but may not improve the psychological issues or access for marginalized populations. Thus, it is necessary that we continue advocating for our future patients and for our community.