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Message from the Director

Translational medicine is the prevailing paradigm, stemming from evidence-based medicine with the integration of basic and clinical research to advance human health and well-being.

As an exclusively health sciences-focused educational and research institution, embedded within the acute hospital setting, TTMI is uniquely placed to develop and enhance translational research for the benefit of patients and to improve the health and well-being of the community. TTMI’s thematic research priorities reflect the wide diversity of healthcare facilities and needs, locally and nationally.

At TTMI, we recognise that excellence in research is critical to our underpinning philosophy of the acquisition of knowledge to enhance human wellbeing and realise human benefit. The quality of our research in turn enhances our credibility in education and outreach.

TTMI’s strategy of improving human health through translational research is predicated on clinical, laboratory-based and health service research informed by real world clinical bedside problems, and societal and global health challenges.

Our targeted research portfolio is designed to develop improved diagnostics, therapeutics and devices. Our patient centered research tackles important healthcare delivery issues, informs policy and clinical practice, disseminates impactful research, and enhances the quality of education of healthcare professionals.
There are four thematic areas of research prioritised within TTMI. We also collaborate within the University, nationally and internationally to facilitate cutting edge multidisciplinary clinical research.

- Translational Cancer
- Translational Immunology, and Infection
- Genomics of Human Disease
- Nanomedicine and Key Enabling Technologies

Sample Key Enabling Technologies:

- Microscopy
- Immunophenotyping Flow Cytometry
- High Content Analysis
- Immunohistochemistry
- Laser Capture Microdissection
- Functional Genomics
- Next-Generation Sequencing
- Protein Purification / Validation
Translational Cancer

Representative Case Study —
Development of a semi-conductor sequencing-based panel for genotyping of colon and lung cancer by the Onconetwork consortium.

Prof. Orla Sheils

Clinical and Market Need

Personalised Medicine relates to the broader concept of patient centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs. It refers to a medical model using characterisation of individuals’ phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. The ability to select patients for treatment with targeted agents on the basis of specific molecular alterations within their cancer cells has led to novel drugs for molecularly selected patient populations, with a view to improving treatment outcome, while minimising side effects.

Approach

Current approaches to detect numerous mutations in a clinical sample run the risk of the tumor sample being consumed before an actionable variant is uncovered. However, next-generation sequencing (NGS) can assess a broad range of genes in a single test and the consortium designed and validated informative NGS panels based on the Ion Torrent AmpliSeq Technology. The resulting kits allow detection of various types of mutations using as little as 10ng of FFPE DNA. This allows laboratory clinicians to analyze samples that may contain partially degraded or limited tumor material, and generate reportable results from more samples than was previously possible. The panels were verified by leading clinicians from the OncoNetwork Consortium with a focus on colon and lung cancers. Disease driving DNA and RNA mutations and genetic rearrangements that cause fusion transcripts are an important and expanding class of actionable biomarkers in cancer. These new kits enable detection of these aberrations even from samples with low DNA/RNA quantity, quality or integrity, ultimately providing actionable information to a greater number of patients and beneficial insight that may help guide treatment.

Collaborator/Funding Agencies

Oncomine© Solid Tumour DNA Kit
Construct library and prepare template

Oncomine© Solid Tumour Fusion Transcript Kit
Construct library and prepare template
Translational Cancer

Representative Case Study — Promising new small molecule drugs for treating gastrointestinal cancer.

Prof. Jacintha O’Sullivan

Treatment algorithms and survival for colorectal cancer patients have changed dramatically over the past decade due to the advent of molecular targeted therapies such as bevacizumab, an anti-angiogenic therapy. However, response rates to this anti-angiogenic therapy is 40% or less. Therefore, there is a need to develop alternative drugs such as small molecules with potent anti-angiogenic activity and can result in the development of drug resistance.

A drug discovery program led by Professor Jacintha O’Sullivan in TTMi in collaboration with Dr. Breandán Kennedy in UCD have identified and patented a small molecule drug Quininib with potent anti-angiogenic activity. Patent: Quininib is the subject of the patent. Anti-angiogenic compounds, WO 2012/095836, granted Dec 2014.

This study recently published in Scientific Reports has demonstrated that Quininib has strong anti-angiogenic activity in human colorectal ex vivo explants, in zebrafish and mice and mechanistically is a novel anti-angiogenic small-molecule CysLT1 receptor antagonist. Structural analogs to Quininib have revealed they can exert an additive anti-angiogenic response in combination with the current licensed therapy Bevacizumab. Quininib and its analogs may complement current anti-VEGF biological agents and act as novel therapeutic agents for colorectal cancer and others cancers driven by angiogenesis. Through recently awarded Horizon 2020 RISE funding (3DNEONET) and in collaboration with European industry partners, further therapeutic development of those novel drugs is now underway using different model systems to test their clinical utility in the neoadjuvant and adjuvant settings in both colorectal and oesophageal cancers.


Trinity College Dublin

Case Studies

Translational Immunology, Inflammation and Infection

Representative Case Study — Human Pulmonary Immunology.

Prof. Joseph Keane

Clinical Need
So many lung diseases such as Chronic Obstructive Pulmonary Disease (COPD), lung cancer and tuberculosis occur in people's lungs because the local pulmonary immune system has been damaged by insults, such as cigarette smoking, yet the cellular mechanisms underlying these conditions are poorly understood due to limited direct access to human lung tissue. In recent years, investigators at TCD have started exploring how cellular metabolism is the master controller of how immune cells work. Such immune cells can either propagate or prevent important diseases, yet most work is done on animal models. Investigators at the TTMI were the first group to demonstrate the role of immuno-metabolism as a defence against tuberculosis in cells taken from human lungs*.

Partnership
Working closely with the clinical research facility (CRF) at St. James' Hospital, the Trinity based TB immunology research lab is uniquely placed to access human alveolar macrophages donated by volunteers at bronchoscopy on our hospital site. This is exploited to address important clinical questions locally and with international collaborators**.

Approach
In the TTMI, investigators use primary human material to interrogate the role of metabolism in directing the host response to infections (such as tuberculosis). Using high-throughput analysis, as well as a panel of cell biology assays to measure macrophage and cell mediated responses, our group is uniquely placed to map out the immune response of the human lung in health and disease. Our track record in developing new paradigms of host defence has allowed us to screen numerous novel therapeutic approaches - with potential to drive innate and cell mediated responses to support diseased patients with immune defects and lung disease. Our collaboration with the RCSI has led to the development of novel inhal ed micro particle approaches to lung directed therapy.

Translational Immunology, Inflammation and Infection

Representative Case Study — Saving newborns with neonatal sepsis.

European researchers developed a sample-to-result automated system for detecting blood pathogens in infants at the point of care.

Prof. Orla Sheils

Clinical and Market Need

Neonatal sepsis is caused by bacterial pathogens that enter the bloodstream, and the disease remains one of the major causes of infant death worldwide, partly due to short comings in current diagnostics. This potentially fatal disease is characterised by a whole body inflammatory response coupled with the presence of a known or suspected infection. The clinical signs of neonatal sepsis can be non-specific, making it hard to distinguish from other conditions such as respiratory distress syndrome or meningitis. This project was driven by the imperative to develop a rapid and reliable mechanism to deliver prompt diagnosis of seriously ill infants.

Partnership

The International Consortium, led by Dr Daniel Mark in Germany was headed by Prof Orla Sheils and Prof John O’Leary at Trinity College Dublin. The other partners included Rohrer AG, Qiagen and Mobidiag Ltd.

Approach

The EU-funded ASCMICROPLAT (Fast automated multiplex analysis of neonatal sepsis markers on a centrifugal microfluidic platform) project addressed this issue through the development of a novel diagnostic platform capable of performing rapid diagnosis of neonatal sepsis. Briefly, the device allows detection of a biologically relevant panel of neonatal sepsis pathogens and sepsis biomarkers from paediatric serum samples within four hours.

The objective of this work was to realise and clinically validate a fully integrated and automated platform for the detection of neonatal sepsis biomarkers and a panel of sepsis-causing bacteria from serum samples. Centrifugal microfluidics were applied to develop an easy-to-use diagnostic test that can be applied at the point-of-care. Biomarker quantification was conducted by a novel magnetic immuno-PCR approach or by automated enzyme-linked immunosorbent assay (ELISA). Pathogen identification was based on an innovative PCR design that included sample preparation (DNA extraction). The tests were integrated on a rotating test carrier, the ‘LabDisk’ that can be processed on a portable processing device using a specific rotational protocol.

The interdisciplinary consortium included a university hospital, a research institute and three SMEs, who have together extensive experience in all relevant fields ranging from neonatal sepsis diagnostics using PCR based assays, to polymer micro fabrication techniques and microfluidics. This project developed an easy-to-use, fast, automated and conclusive test method, with the potential for significant clinical and market impact in the diagnosis and management of neonatal sepsis.
Translational Immunology, Inflammation and Infection

Representative Case Study — Interrogating T cell migration — a High Content Analysis approach.

Prof. Aideen Long

The continuous re-circulation of T lymphocytes between the blood and lymphatic systems and the localised recruitment of antigen-specific T cells to sites of inflammation is crucial to the surveillance and effector function of the immune system. At the same time, unregulated recruitment of T lymphocytes into inflamed tissues may result in autoimmune disease, leading to tissue damage and/or debilitating illness. T lymphocytes are considered to be key players in several autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis and psoriasis. Over the past two decades, the signalling pathways and enzymes that control T lymphocyte migration have been the subject of intense scrutiny, mainly because of the promise that understanding the roles of these pathways in biology may provide novel targets for the manipulation of immunological responses, including anti-inflammatory therapies.

Prof. Long and her research team have utilized siRNA and pharmacological libraries in combination with high content analysis (HCA) to identify novel signaling pathways or enzymes involved in T cell migration. Image-based HCA is a technology that is ideal for the analysis of complex cellular phenotypes, as the automated image acquisition permits large cell populations to be rapidly analysed on a large scale. Furthermore, 10’s – 100’s of descriptive features or parameters can potentially be extracted from each cell, thereby enabling multi-dimensional analysis of cellular phenotypes. In these studies, the ability of the inhibitor (siRNA or pharmacological) to modulate T cell polarity and migration in response to stimulation through the LFA-1 integrin was measured using HCA. The cytoskeletal elements (actin and microtubule) of the cells (+/- inhibitor) were immunofluorescently stained permitting multiple measurements of cell/cytoskeletal shape and intensity. This was followed by complex analysis of multiple parameters and hierarchical clustering which facilitates the elucidation of specific pathways involved in the regulation of lymphocyte migration.
Translational Immunology, Inflammation and Infection

Representative Case Study — Trinity Health Kidney Centre – Unlocking the potential of patient registries and biobanks.

Prof. Mark Little

Clinical and Market Need
As part of the Trinity Health Kidney Centre, this TTMI research unit is a basic science facility uniquely placed to address clinical questions of importance pertaining to kidney diseases. Under the leadership of Prof. Mark Little, Trinity Health Kidney Centre is an academic health science centre that incorporates the clinical services in Tallaght and St James’s Hospitals.

This highly successful endeavour has exclusive access to longitudinal data and samples from many well-phenotyped patients through the Irish Rare Kidney Disease Registry and Biobank, and the material available has led to the development of exciting new biomarkers of kidney disease.

The group have shown that soluble CD163, as measured in urine of patients, correlates well with the level of inflammation caused in active renal vasculitis and displays excellent biomarker characteristics.

Partnership
In view of the strong clinical background of the group and collaborations with the CRF, there is governance, oversight and due diligence which allows for the safe application of human materials to addressing crucial clinical research questions.

The development, from scratch, of new biomarkers for kidney disease has been taken to patent submission, and formal industrial collaboration. The group’s leadership is manifest in European fora that seek to advance new paradigms of how best to manage patients with devastating vasculitis.

Approach
Considering the clinical and scientific remit of the group, they are uniquely placed to engage in translational medicine and nephrology. Such endeavours deliver real advances in precision medicine where patients can be treated, but only when these new tests are supportive. Such endeavours also avoid the use of treatments in patients where they are no longer indicated. Research efforts are enhanced by a combination of clinical access to material from kidney patients and cell and molecular biology excellence on the same campus, coupled with deep phenotyping in patients. Furthermore the group has a track record in leading international collaborations and grant funding endeavours which seek to establish new biomarkers of kidney disease.

Collaborator/Funding Agencies

Staining of the glomerulus to define expression of the macrophage marker CD163 (red), which is detectable in the urine in active glomerulonephritis.

Genomics of Human Disease

Representative Case Study — Understanding the genetic etiology of mental disorders.

Prof. Aiden Corvin

Clinical and Market Need
Mental disorders are significantly heritable, common and across the lifespan make a disproportionate contribution to societal disease burden. Conditions like autism or schizophrenia are diagnosed based on clinical symptoms and the range of effective treatments is limited. Recent advances in genetics offer new approaches to understanding the biology involved to improve diagnostics and identify novel therapeutic approaches.

Partnership
Profs. Aiden Corvin & Michael Gill were founder members of the Psychiatric Genomics Consortium (PGC) and have worked with international academic partners to understand the genetic basis of these disorders.

Approach
Using methods based on genome-wide association study (GWAS) arrays we have identified common and rare genetic variants that contribute to schizophrenia risk in the Irish population. We have also made a substantial contribution to international efforts which have now identified more than 150 common risk loci for these conditions. Applying pathway-based analytic methods we have shown the important role of neuronal cell adhesion, membrane scaffolding and chromatin remodeling in schizophrenia, and possibly more widely in other disorders. We are currently leading an international family-based whole genome sequencing study funded by NIH/SFI and working with academic partners on other large-scale studies in schizophrenia and bipolar disorder. This experience and our recent successful SFI Research Infrastructure award will be important in developing a flexible core facility to support genomics research across human diseases.

Collaborator/Funding Agencies
Genomics of Human Disease

Representative Case Study — Genomics core facilities – TrinSeq.

Dr. Elaine Kenny

Funded through the 2008 SFI-Research Infrastructure Call, Trinseq was Ireland’s first next-generation genome sequencing (NGS) facility set up by Dr Elaine Kenny and Dr Derek Morris. What started out as a core equipment purchase to aid in the research activities of the Neuropsychiatric Genetics Research group lead by Professor Michael Gill has developed into a core facility and is supported with a highly skilled team that provides numerous resources for its many users throughout Ireland. The facility currently houses an Illumina MiSeq platform and is self-sustaining with a proven track-record in research and partnership with Science Foundation Ireland (SFI) funded researchers, the wider all-Ireland research community and industry. The facility supports diverse projects from determining organisms that define soil composition (metagenomics) or cause disease (e.g. food-borne pathogens); to identifying ancient human DNA; to finding genetic mutations in living people that contribute to conditions as disparate as autism, arthritis and cancer. The facility and its core staff lead by Dr Elaine Kenny have been co-authors or acknowledged on numerous publications in many diverse areas reflecting the diversity of the projects it supports.

In 2010 TrinSeq founded the Irish Next Generation Sequencing Meeting to provide education and foster cross institutional, industrial and international collaboration with delegates spread across Ireland. This 1 day meeting has earned a great reputation as being a valuable source of education, information and networking to the wider NGS community. The 2016 meeting attracted > 200 delegates from academic, clinical and industry backgrounds.

More recently, Professor Aiden Corvin and Dr Elaine Kenny were successful in their bid for strategic funding to purchase a much higher throughput sequencing technology with SFI for the facility. This new equipment will help to broaden the type and scale of projects that can be facilitated through the facility and in particular allow development and further engagement with industry and clinical partners that have a need for higher throughput sequencing combined with a highly skilled local support team. TrinSeq has also been a partner to Enterprise Ireland to provide high skilled sequencing projects and data analysis to SME business’ under their Innovation voucher scheme highlighting the translational aspect of the work carried out and possible through the core facility.

13 years
Time taken to complete The Human Genome Project.

10 days
Time taken for TrinSeq to generate the same amount of data in 2014.

276
Number of human genome equivalents sequenced by TrinSeq in 2014. TrinSeq has sequenced the equivalent of a human Genome a day.
## Key Enabling Technologies

### Nanomedicine

#### Representative Case Study — From bench to bedside.

**Prof. Yuri Volkov and Prof. Adriele Prina-Mello**

The growing interest in the medical application of nanotechnology from academic and industrial researchers worldwide has led to the development of novel nanomedical platforms and nanodrugs, attracting substantial investments. Nanomedicine and its translation has evolved in recent years with enhanced sensitivity, safety and efficacy over existing diagnostic, treatment and combination strategies, resulting in clear benefits for the patient and society.

Prof. Yuri Volkov and Prof. Adriele Prina-Mello have pioneered the development of nanotechnological toolkits for multi-modal disease diagnostics and treatment monitoring (NAMDIATREAM project). As part of the Multifun consortium, the group developed functionalised nanoparticles for early stage detection and treatment of breast and pancreatic cancer, where cancer stem cells are the key target. Additionally, Prof. Yuri Volkov and Prof. Adriele Prina-Mello are also involved in the Advanced Materials for Cardiac Regeneration (AMICARE) project.

TTMI is central enabling partner in the H2020 infrastructure project aimed at establishing the EU NanoMedicine Characterization Laboratory (EU-NCL), which partners with the US-NCL (as part of the National Cancer Institute) in the field of advanced characterisation, industrial translation and future market approval of nanomedical products.

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**Enabling the increase of technology readiness level**

Nanoparticle internalisation: Gold nanoboxes (AuNBs) interacting with adenocarcinoma cell line (A549) after 24 h exposure. Confocal micrographs of A549 cells exposed to AuNBs and stained with rhodamine phalloidin (F-actin, in red) and Hoechst 33342 (nuclei, in blue). AuNBs localisations were imaged in confocal reflectance mode and are shown in green as pseudo-colour. Reference: Movia D., et al., Volkov A. and Prina-Mello A., Biomaterials 2014.
A synergistic relationship between TTMI, SJH and industry is key to ensuring the continued development and commercialisation of new healthcare therapeutics and innovations. TTMI and SJH are committed to a clinically orientated solutions approach to research that will drive improvements in patient outcomes. Hence, we welcome opportunities to foster industry collaborations to expedite healthcare research, while concurrently, facilitating access to leading scientific and medical talent. As exemplified in the case studies, TTMI has a wealth of experience developing enterprise collaborations, and therefore, is well placed to advise and capitalise on various national and international support initiatives.

The scope of enterprise involvement can take many forms, and the following is a brief summary of past engagements:

- Equipment and Core Facility Access
- Collaborative Research
- Consultancy
- Licensing Agreements
- Contract Research / Innovation Vouchers
- Innovation Partnerships
- Horizon 2020

Trinity Translational Medicine Institute has strategically consolidated research teams into the four thematic areas; and thus, an exceptional array of scientific and medical talent are forging new frontiers in translational medicine.

Please consult our website www.tcd.ie/ttm for further details on the vast array of clinical and translational research activities.