I am delighted to introduce the latest edition of our breast cancer research newsletter which highlights our activities and achievements over the past year. The National Breast Cancer Research Institute is over 20 years in existence and its research facility is based in the Discipline of Surgery, National University of Ireland Galway.

Breast cancer accounts for the greatest number of female cancers diagnosed in Ireland. It is the second highest cause of cancer death in Irish women. Thanks to the emphasis on early detection provided by awareness campaigns, BreastCheck screening and the development of designated national cancer centres, major advances in the diagnosis, treatment and monitoring of breast cancer have been made.

NBCRI researchers are fortunate to work closely with the clinical breast cancer team at University Hospital Galway and academic research colleagues at NUI Galway as well as national and international collaborators. Over the past decade our group has been remarkably fortunate to be able to develop high quality research programmes, in particular the study of microRNAs in breast cancer and the role played by mesenchymal stem cells in tumour targeting. The effects of our research are felt nationally and globally. In the past year our international collaborations have yielded high impact publications in breast cancer genetics (Nature Genetics, April 2013) and breast cancer surgical management (Annals of Surgery, August 2013).

This newsletter includes a focus on the NBCRI funded Summer Research School, the Cancer Biobank and our collaboration with the Biostatistics Unit at NUI Galway.

Construction commenced on the Translational Research Facility in September 2013. This development has received a major boost from a €1 million NBCRI donation to the Galway University Foundation. This modern, functional facility will enable us to develop our own research field and expand our collaborative work.

The Discipline of Surgery hosts the annual Sir Peter Freyer Surgical Symposium, the largest surgical conference in Ireland. There is a breast cancer research and clinical session at this meeting which is attended by many of the leading breast surgeons and researchers in Ireland. This gives stage for our team to present new, exciting and ground breaking research to our colleagues nationally and internationally.

The NBCRI is largely funded from voluntary fundraising activities. I would like to thank you, our supporters, for your time and generosity, allowing this vital research to be carried out so that patients can be best served now, and in the future. As ever, help is always needed so please continue to support Breast Cancer Research by donating what you can.

Michael J Kerin
MCh, FRCSI, FRCSEd, FRCSGen
Professor of Surgery & Research Director of NBCRI

The NBCRI has donated €1 million to the Galway University Foundation for the development of the Translational Research Facility. Pictured are current and past directors of NBCRI with NUI Galway President, Dr James J. Browne.

<table>
<thead>
<tr>
<th>PhD</th>
<th>MD</th>
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<tr>
<td>Ronan Glynn</td>
<td>Niamh Hogan</td>
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<td>Helen Heneghan</td>
<td>Peadar Waters</td>
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<td>Elrasheid Kheirelseid</td>
<td>Jemima Dorairaj (pictured)</td>
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<td>Marion Hartmann</td>
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<td>James Ryan</td>
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**WHY DO WE RESEARCH?**

Breast cancer is a complex disease - there are many types of the cancer. The choice of treatment given to a patient depends on the type of breast cancer they have. How a patient responds to treatment may also depend on the type of breast cancer they have.

The cause of breast cancer and how it spreads and responds to treatments is not fully understood. Today we have breast screening to detect breast cancer early in its development and treatments have been advanced and altered to meet the emerging subtypes of cancer that are diagnosed.

The key to understanding the biology of cancer lies in research. Much of our research focuses on the search for a single or multiple **biomarker(s)**: a substance in blood or tissue that can be measured and evaluated as an indicator of either normal breast biology, the presence of disease or a patient’s response to therapy.

**A biomarker can be:**
- A mutation in a patient’s inherited genetic code (DNA)
- An abnormally expressed protein or RNA molecule that can alter how cells function

**The discovery of a breast cancer biomarker can lead to the development of:**
- Non-invasive, sensitive methods for early detection of a breast tumour or a metastatic tumour (cancer that has spread beyond the breast)
- Specific targets for cancer treatments – gene therapy, chemotherapy etc.

**CANCER BIOBANK**

Since 1990 the Discipline of Surgery has developed a cancer biobank with the financial support of NBCRI. Since its inception this resource has proved invaluable to our research team. The Cancer Biobank has received ethical approval from the Galway University Hospitals Clinical Research Ethics Committee and patients who volunteer to donate their samples are requested to sign an approved consent form.

This collection of clinical samples is vital for our researchers to be able to investigate the various biological markers of cancer. The samples stored in our biobank are used by researchers in the breast cancer laboratory and our official collaborators at national and international research institutes. Samples are collected from patients from several hospitals in Ireland – Beaumont and St James’ in Dublin, Sligo, Mayo, Letterkenny, and Galway. To date we have specimens from approximately 5000 patients. These specimens include blood and/or tissue samples. All samples are codes and anonymised before low temperature storage.

**How funding can help develop our Biobank**
- Designated staff to manage the daily biobank operations
- Maintenance of equipment – freezers, fridges, security monitoring of these pieces of equipment
- Purchase of Consumables – plastic tubes, boxes, labels, racks
- Software – our biobank inventory is managed by a designated laboratory database. Upgrades and technical support for this software programme are required.
- Administrative costs involved in maintaining our biobank to international standards

**RESEARCH ACHIEVEMENTS**

Sonja Khan received a Health Research Board bursary to attend the National Cancer Institute Molecular Prevention Course in Washington DC in 2013.

Undergraduate students, Lauren Hughes and Lua Rahmani, received Wellcome Trust Student Scholarships and Una McVeigh and Mahrukh Azhar received Health Research Board funding for their summer student research in 2013.
Breast Cancer is the most common cancer among women and the genetic cause of breast cancer is the source of much enquiry. The discovery of high risk mutations in BRCA1 and 2 genes in the 1990s identified the cause of breast cancer in approximately 3% of the population. A further series of investigations have implicated moderate risk genes and a new series of studies have now identified 41 new low penetrance breast cancer susceptibility alleles.

This latest study, published in Nature Genetics in April 2013, is an extensive analysis of 10,052 breast cancer cases and 12,575 control cases of European ancestry. The results analysed more than 200,000 SNPs (single nucleotide polymorphisms) and showed that 41 of these are strongly associated with breast cancer susceptibility. In addition, genetic links between breast, prostate and ovarian cancer were identified. This represents a great advance in our understanding of these cancers which together affect more than 2.5 million people worldwide annually.

The study which is a collaboration involving multiple international research centres and genetic consortia is the largest genetic association study in cancer so far. Professor Michael Kerin and Dr Nicola Miller contributed to the study.

HOW DOES YOUR DONATION FUND BREAST CANCER RESEARCH?

The NBCRI research laboratory is funded primarily by voluntary fundraising activities. Funding is vital to support the following aspects of research:
HOW BREAST CANCER RESEARCH HAS INFLUENCED MY CAREER?

Dr Helen Heneghan, MB MRCS PhD, started her research in 2008 as an NBCRI-funded postgraduate. She went on to receive a Clinical Research Fellowship from the Health Research Board and was awarded her PhD in 2012. Helen spent two years working at the Cleveland Clinic, Ohio and is currently working as a General Surgery & Hepatobiliary Specialist Registrar at St. Vincent's University Hospital, Dublin.

"Researching in the NBCRI laboratory opened up a world of professional opportunities for me. It permitted me to travel and meet world leaders in the field of breast cancer translational research. This initiated several important collaborations between the Discipline of Surgery at NUI Galway and prominent academic centres in the USA and UK including Yale University in Connecticut, Baylor College of Medicine in Texas, and The Institute of Cancer Research in London. I have also been able to apply the techniques and knowledge gained from my breast cancer research to other disease processes, to come to a better understanding of several other prevalent illnesses and cancers. Additionally, I learned to appraise and critique scientific literature and use the information within to formulate evidence-based treatment plans for patients with a variety of diseases including breast cancer. My experience with the NBCRI has been beneficial in furthering my career to date, and has created an excellent foundation to help me reach my goal of becoming a leading academic surgeon in Ireland."

BIOSTATISTICS & BREAST CANCER

Biostatistics is the application of statistics to problems in the biological sciences, health, and medicine. Statisticians are vital to all forms of health care, from developing treatments to examining regimens for preventing and detecting disease. The risk of a woman developing breast cancer, for example, may be related to family history, environment, or behaviour. To deal with the complexity of the human body and its interactions with its surroundings and to understand and untangle these complexities requires sophisticated statistical methods. Statisticians in the Biostatistics Unit are working closely with the NBCRI researchers to extract information from collected data to develop powerful risk assessment tools to predict a woman's chance of developing breast cancer. Such a tool will guide recommendations for screening for early disease detection leading to new novel treatments that will reach the public more quickly.

Dr John Newell (right) is Senior Lecturer in the School of Mathematics, NUI Galway and leads the Biostatistics Unit at the HRB Clinical Research Facility

RESEARCH AREAS

MicroRNA Expression in Breast Cancer
MicroRNAs are tiny RNA molecules that have the ability to regulate the activity of other genes. Our research has shown that miRNAs are detectable and stable in the blood of breast cancer patients, indicating their potential as biomarkers.

Breast Cancer Population Genetics
BRCA1 and BRCA2 are the two main genes associated with breast cancer risk. Among the Irish breast cancer population there are many women with a family history of breast cancer who do not carry mutations in either of these genes. Our research aims to investigate the scientific suggestion that several common low penetrance genes account for the non-BRCA genetic susceptibility to breast cancer.

Mesenchymal Stem Cells & Breast Cancer
Adult Mesenchymal Stem Cells (MSCs) have the ability to home to the site of tumours and metastases, and appear to bypass the immune system. Understanding the biology of MSCs and their interactions with breast cancer cells is fundamental to determining whether these cells can be safely harnessed for tumour-targeted delivery of therapeutic agents.

Tumour Microenvironment in Breast Cancer
It is well established that within the breast tumour microenvironment, tumour epithelial cells coexist with stromal fibroblasts. Stromal cells are not simply innocent bystanders at breast cancer sites. Current studies in the laboratory aim to determine how stromal cells function within the primary tumour microenvironment, identifying factors secreted and their impact on epithelial cell gene expression and function.
Dr Maria Costello MB BCh BAO undertook a NBCRI Summer Research Scholarship in 2009. She returned to the lab in summer 2010 to continue her research under the supervision of Dr Róisín Dwyer. Maria was awarded her degree in Medicine in 2012 and is starting her Medical Training Scheme next year.

“I applied to do a summer research project in the laboratory as an undergraduate medical student and enjoyed it so much I came back the following year to do a second project! What appealed to me the most was the hands-on experience of the projects, the expert supervision and the pleasant work environment. During my time in the lab, I was taught a variety of scientific techniques by experienced researchers who were very supportive. Additionally I was given a great introduction and foundation in the research world, from the logistics of setting up a project, to result analysis and presentation. Not only did I gain these new skills, but I also had the opportunity to present at a number of conferences and collaborate on a publication. The valuable experience I have gained has benefited me greatly and has motivated me to partake in postgraduate research opportunities in clinical practice.”

Lua Rahmani, Medical Student Lua was awarded a Wellcome Trust Student Scholarship for a summer research project in 2013. She was supervised by Claire Glynn and Dr Róisín Dwyer.

“As an undergraduate medical student, I had learned to study and appreciate the dynamic nature of scientific research and its impact on the practice of medicine on a conceptual and theoretical basis. Within these short eight weeks however, I was provided with the opportunity to explore the fascinating and ever-advancing field of cancer research on a very practical level. The opportunity to gain crucial first-hand experience and such a great wealth of scientific techniques in a dynamic and motivated environment alongside truly hard-working, enthusiastic and highly-skilled professionals was inspiring. Acquiring a greater understanding of the importance of clinical research at a stage so early on in my career is invaluable as it has focused the lens through which I view my studies and my future career within the medical profession. Being of the belief that we should ever-strive to contribute to the welfare of humanity and to the advancement of civilisation, this project has been a direct means whereby I could contribute to something greater than myself and I hope that research of this nature will become an integral part of my future career.”

Students from the Masters (MSc) in Regenerative Medicine undertake a five month research project for their thesis. In 2013 Killian O’Brien did his project entitled “Loss of MicroRNA-504 Expression is Associated with Breast Cancer” in the NBCRI laboratory under the supervision of Dr Róisín Dwyer. Previous students from this MSc course, James Ryan and Sonja Khan, have gone onto to do their PhDs with the breast cancer research group.

Killian is pictured presenting his research poster to the MSc Regenerative Medicine examiners in August 2013.

MASTERS IN SURGERY

The research laboratory hosts the Surgical Lab Skills module of the Masters in Surgery (MCh), a taught, part-time course offered by NUI Galway. The postgraduate class, made up of surgical trainees, took part in laboratory practical classes over two weekends in March 2013. Topics covered included RNA Extraction, PCR Preparation, immunostaining and cell culture techniques. www.mastersinsurgery.com
Sonja Khan, PhD Student
Sonja has completed her laboratory research and writing up her PhD thesis. Her research investigation has been on the levels of specific microRNAs in breast tissue. She has also analyzed a potential relationship between these specific microRNAs and genes known to regulate crucial processes in breast cancer progression.

Dr Ailbhe McDermott, PhD Student
Ailbhe is the first recipient of the NBCRI Tricia McCarthy Memorial Fellowship and is currently writing up her PhD thesis. Her research focused on circulating miRNAs profiles in breast cancer, particularly within the Luminal-A cancer subtype. She also examined whether the circulating miRNA profile changes over the course of neoadjuvant chemotherapy.

Claire Glynn, PhD Student
Claire is in the 3rd year of her PhD studies. Her research focuses on the recent and exciting developments made in the field of intercellular communication within the tumour microenvironment. It is suggested that microRNAs travel from one cell to another in protective vesicles called exosomes, thereby allowing delivery of genetic information. Claire received a James Hardiman PhD Research Scholarship in September 2011.

Deirdre Wall, PhD Student
Deirdre is undertaking her PhD in Biostatistics under the supervision of Dr John Newell at the HRB Clinical Research Facility, NUI Galway. She is the current recipient of the NBCRI Anne Ryan Memorial Fellowship. Deirdre’s PhD involves developing statistical techniques to identify clinical and pathological variables that can predict survival time and disease recurrence for breast cancer patients. She has developed new statistical methodology which she presented at the International Society for Clinical Biostatistics Conference.

Cathy Brougham, PhD Student
Cathy is in the first year of her PhD and is investigating the role of adipose-derived microRNAs in breast cancer. Mesenchymal Stem Cells (MSCs) are found within breast tumours and have the ability to develop into adipose cells. microRNAs secreted by MSCs, and their impact on tumour cells, is of particular interest. This is a novel and exciting field of research.

Dr Terri McVeigh, PhD Student
Terri is in the second year of her PhD concentrating on Population Genetics, specifically, inherited susceptibility to Breast Cancer. As part of her research Terri has visited our collaborating lab in Yale University twice in 2013.
**Dr Marese Murphy, MD Student**

Marese is in the second year of her MD research degree. Her work is focusing on the patterns of microRNA expression in the circulation of patients with breast cancer, looking at specific breast cancer subtypes and the prediction of response to treatment. She also plans to validate microRNAs studied previously in external cohorts of patients to further assess their diagnostic accuracy and future potential.

**Dr Maire Caitlin Casey, MD Student**

Maire Caitlin joined the research team in July 2013. She has begun analysing circulating microRNAs in the blood of breast cancer patients who are receiving neoadjuvant therapy. The aim of her research is to identify specific microRNAs that may be used as biomarkers. This discovery would enable development of tailored patient treatment plans, assessment of response to treatment and guide overall prognosis.

**Dr Doireann Joyce, MD Student**

Doireann completed Basic Surgical Training in 2012. She has commenced an MD focusing on the clinical and pathological characteristics of basal subtype breast cancer, with the aim of individualising treatment for this group of patients. She aims to pursue higher surgical training upon completion of her research.

**Dr Cillian Clancy, MD Student**

Cillian has completed basic surgical training and joined the research team in July 2013. His research will focus on determining how cells communicate with each other in the tumour micro-environment, looking specifically at Mesenchymal Stem Cells (MSCs) and the role of miRNAs in cell communication.

**Catherine Curran and Emer Hennessy** are the Senior Technical Officers in the Research Laboratory. They are responsible for the day to day management of the lab facilities. They coordinate the Research Biobank and the Breast Cancer Database and provide student training and research administrative support.

### Research Collaborations

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<tr>
<th>International</th>
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<tbody>
<tr>
<td>The Mayo Clinic, Minnesota, USA</td>
<td>BREAST-PREDICT Collaborative Cancer Research Centre</td>
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<tr>
<td>University of Arizona, USA</td>
<td>Biomedical Diagnostic Institute, Dublin City University</td>
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<tr>
<td>Baylor College of Medicine, Texas, USA</td>
<td>Regenerative Medicine Institute (REMED)</td>
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<tr>
<td>Yale University, Connecticut, USA</td>
<td>National Centre for Biomedical Engineering Science (NCEBS)</td>
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<td>Wellcome Trust for Human Genetics, Oxford, UK</td>
<td>Marine Institute</td>
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<tr>
<td>NHS Cancer Screening Programmes, UK</td>
<td>All Ireland Cooperative Oncology Research Group (ICORG)</td>
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<tr>
<td>Nottingham Trent University, Nottingham, UK</td>
<td>NUI Galway – Schools of Psychology, Economics, Physics, Natural Sciences, HRB Clinical Research Facility, Molecular Diagnostic Research Group, Whitaker Institute</td>
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A SELECTION OF RECENT RESEARCH PUBLICATIONS