National Research Ethics Service

NHS Health Research Authority

RESEARCH TISSUE BANK / BIOBANK

Annual Report to Research Ethics Committee

Research tissue banks / biobanks with approval from a Research Ethics Committee are required to provide the REC with an annual report on their activities. This form sets out the minimum content of the report and a template format, which may be adapted appropriately.

1. Details of Tissue Bank Manager

Name:	Dr Claire Lewis (NIB Operational Manager) Mrs Priscilla Clark (NIB Administrator)
Address:	Northern Ireland Biobank Centre for Cancer Research & Cell Biology Queen's University Lisburn Road Belfast BT9 7AB
Telephone:	028 9097 2915
E-mail:	nibiobank@qub.ac.uk

2. Details of the bank

Title:	The Northern Ireland Biobank
Establishment responsible for management of the bank:	Queen's University Belfast
HTA licence number: *(where applicable)*	12044
Designated Individual: *(where applicable)*	Dr Jacqueline James
Main REC:	OREC (NI) HSC NI REC 1 committee
REC reference number:	16/NI/0030

3. Summary of activity for the period 1.04.2016 – 31.03.2017

Please provide an overall summary of the bank's activities during the year, including:

- *Donor recruitment and sample collection*
- *Release /use of samples*
- *Collaborations with other banks /programmes*
- *Donor engagement and publicity*
- *Any significant developments in the bank's scope, operation or governance.*

DONOR RECRUITMENT

TOTAL NUMBER OF PARTICIPANTS CONSENTED = 1849*
TOTAL NUMBER OF PARTICIPANTS REFUSED = 95
*** *FFPE blocks from these patients are retrieved from NHS Histopathology after diagnostic process has been completed.***

PROSPECTIVE TISSUE SAMPLE COLLECTION AS OF 28 March 2017

SOLID TUMOURS

COLLECTION PROTOCOL	**Total Donors**
BREAST (neoplastic)	795
BREAST (high risk of malignancy)	29
COLORECTAL	385
PROSTATE	134
GYNAE (neoplastic)	344
GYNAE (non-neoplastic)	101
LUNG	14
Upper GI	30
Head and Neck	17
OVERALL	**1849**

HAEMATOLOGICAL MALIGNANCIES

Total banked 545:
500 (bone marrow), 2 (peripheral blood), 43 (uncertain BM or PB)

RETROSPECTIVE TISSUE COLLECTIONS

NIB has facilitated retrieval of over 12,000 surplus formalin fixed paraffin embedded (FFPE) tissue blocks from cases held in BHSCT Tissue Pathology archives.

ANONYMISED SAMPLES RELEASED TO RESEARCHERS
1 APRIL 2016 – 28 March 2017

SAMPLES RELEASED TO RESEARCHERS	
SAMPLE TYPE	**NUMBER OF SAMPLES**
FRESH TISSUE FOR CULTURE (inc ascites)	60
FRESH FROZEN TISSUES	72
BLOOD DERIVATIVES	171
TISSUE MICROARRAY SECTIONS (TMAs)	750
SLIDES FOR DIGITAL SCANNING	2500
SLIDES FOR NUCLEIC ACID EXTRACTION	250
RNA ALIQUOTS	80
DNA ALIQUOTS	32
TOTAL SAMPLES RELEASED	**3915**

In total, as of March 2017, NIB has released to researchers approximately 34224 subsamples. The BHSCT FFPE

samples associated with NIB researcher applications have been made available, anonymised, to researchers for specific 'scientifically reviewed' projects.

COLLABORATIONS WITH OTHER BANKS/PROGRAMMES

NIB is registered on the UKCRC Tissue Directory and is a member of the European Society for Biobanking and Biopreservation (ESBB) and the International Society for Biological and Environmental Repositories (ISBER).

The NIB Operational Manager is a member of the newly formed European Society for Biobanking and Biopreservation (ESBB) working group on science and innovation.

NIB participates in the Integrated Biobank of Luxembourg's (IBBL) proficiency testing schemes.

ISBER have developed a self-assessment tool that highlights areas that a biobank may need to focus on to improve its operating procedures, based on responses around possible risk of specimens. NIB's risk-balanced assessment score was 91% and all areas of non-conformity have been addressed where possible.

NIB regularly hosts visitors, for example from the UKCRC Tissue Directory, Dublin biobank, The Leeds Bone Cancer Research Trust and the Galway HRB Clinical Research Facility. NIB hosted a Prostate Research Nurse from Kings College London on Friday 11 November as part of an ECMC Cross Centre Placement. Members of the Northern Ireland Assembly Health Committee visited on 17 November 2016.

NIB staff have made visits to other biobanks, most recently to the NHS Research Scotland GGC Biorepository.

DONOR ENGAGEMENT AND PUBLICITY

NIB staff are facilitating teaching and learning on the new MSc in Molecular Pathology course at Queen's University which started in September 2016.

NIB had a stand at the Northern Ireland Capability Exhibition on 6 October 2016 at Riddell Hall. This was the second year of this event which is organised to allow Northern Ireland to showcase its capabilities in Clinical Research to senior medical and scientific staff from a range of research based pharmaceutical companies.

NIB took part in the second Cancer Research Open Day at Queen's University, hosted at the Centre for Cancer Research and Cell Biology on Saturday 22nd October 2016. This event attracted hundreds of visitors of all ages and allowed members of the public to see first-hand how NIB facilitates cancer research. NIB staff were on hand to provide tours of the biobank facility and Dr Jackie James led a Conversation Hub 'What's the Issue with your Tissue?'

NIB was one of six finalists shortlisted for the 2016 UK Biobank of the Year award. This award recognised Biobanks that have gone above and beyond in facilitating ground breaking research with nominations made by researchers who have benefited from their services. Finalists were shortlisted based on their contribution to the nominator's research, how the biobank made their research possible and other factors including access to samples, quality and service. The NIB was nominated by Dr Helen Coleman from the QUB Centre for Public Health.

NIB were nominated for the QUB Staff Excellence 'Team of the Year' award. All nominees were invited to attend the QUB Awards Ceremony in the Whitla Hall on 3 February 2017.

NIB has established a twitter account (https://twitter.com/nibiobank)

Meetings Attended

NIB Operational Manager and 2 Biomedical Scientists attended Europe Biobank Week in Vienna from the 13 – 16 September 2016 and had two poster presentations on ' NIB: the first five years' and 'Quality Control Experiments'.

The Deputy Scientific Director and Operational Manager met with the Pathology Managers (Belfast Trust, Southern Trust, Western Trust and Northern Trust) on Wed 27 July 2016. They were given a tour of the laboratory and biobank storage area and NIB responded formally to questions which had been tabled beforehand.

The NIB Scientific Director and Operational Manager made a presentation to the Pathology Network Board on 11 October 2016.

The NIB Operational Manager and a biomedical scientist attended the Confederation of Cancer Biobanks & CM-Path Conference 'Working together: Collaboration in Cancer Biobanking' in Glasgow on 17 October 2016.

The Deputy Scientific Director and Operational Manager made a presentation to the HSC Chief Executives' Forum on 7 November 2016.

The NIB Deputy Scientific Director and Operational Manager attended the UK Biobanking Showcase on 16 November 2016 in London where participants voted for the winner of the 2016 UK Biobank of the Year.

Conference Proceedings & Publications

The Northern Ireland Biobank: the first 5 years. Lewis C, McQuaid S, James J. Europe Biobank Week, 13 – 16 September 2016, Vienna. Poster Presentation.

Northern Ireland Biobank Quality Control Experiments. Greene C, O'Doherty E, Lewis C, James J, McQuaid S. Europe Biobank Week, 13 – 16 September 2016, Vienna. Poster Presentation.

Building a 'Repository of Science': The importance of integrating biobanks within molecular pathology programmes. Claire Lewis, Stephen McQuaid, Peter W Hamilton, Manuel Salto-Tellez, Darragh McArt, Jacqueline A James. European Journal of Cancer, 67 (2016) 191 – 199.

4. Amendments

Have any substantial amendments been made during the year?	**Yes**
If yes, please give the date and amendment number for each substantial amendment made.	01 Substantial Amendment, 20 July 2016

5. Applications for release of samples

Summary of approved projects (up to 31 March 2017)

Reference:	**NIB15-0166**
Chief Investigator:	**McDade, Simon**
Title:	**Characterizing p53 family, co-factors, targets and de-regulation in Head and Neck Squamous Cell Carcinoma**
Sponsor:	**QUB**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**23/03/2017**

Summary

Squamous cell carcinomas (SCC) arise from the epithelium of skin, cervix, uterus, anus, Pancreas, oesophagus and the head and neck, which have poor prognosis and highly toxic frontline therapies which incur significant long-term effects on quality-of-life. Currently there are extremely limited options for biomarker-guided, molecular-targeted therapies i; and for those available such as EGFR inhibitors, determining who will benefit is unclear because of a poor understanding of the disease at the molecular level. This research aims to utilise comprehensive genomic analysis of mutation, Gene expression and methylation and integrating this with molecular, morphology and digital pathology analyses of SCC patient cohorts to identify predictive and prognostic biomarkers. Not only will this provide novel insights to the stratification of SCC patients, which could be exploited for diagnostic or therapeutic application. But also enable our long-term goal of developing novel therapeutic strategies to exploit p53 family dysfunction-induced vulnerabilities in these poor prognosis cancers.

Reference:	**NIB15-0175**
Chief Investigator:	**Kelly, Paul**
Title:	**Expression of TLE-1 in non-mesenchymal neoplasms. A TMA-based study**
Sponsor:	**Belfast Health & Social Care Trust**
Location of Research:	**Pathology Laboratory, Royal Victoria Hospital**
Date of Approval:	**10/12/2015**

Summary

Synovial sarcoma (SS) is a malignant mesenchymal neoplasm that accounts for 5 – 10% of all soft tissue sarcomas. It was initially recognized as a biphasic neoplasm with both epithelial and mesenchymal components but it is now clear that there is considerable morphological and immunohistochemical heterogeneity. Although the two cell components of SS may differ, morphologically they are regarded as histogenetically similar. Difficulty can arise in the diagnosis of SS owing mainly to morphological similarity to other soft tissue tumours for example solitary fibrous tumour (SFT) and malignant peripheral nerve sheath tumour (MPNST). In addition, SSs with predominant epithelial elements may be confused with carcinomas and vice versa. Synovial sarcoma is defined by the presence of the t(X;18)(SS18-SSX1/2) translocation and ancillary molecular techniques have become the gold standard for diagnosing these tumours. However such techniques are expensive and not widely available. In the past although carefully selected immunohistochemical panels were used to aid the diagnosis of SS, no marker was totally specific or sensitive and, like morphology, overlap existed with known mimics. To this end interest focused on the development of novel immunohistochemical markers. The immunohistochemical marker Transducer-like enhancer of split 1 (TLE1) has been identified from genetic profiling studies to be consistently overexpressed in SSs regardless of subtype. Initially considered highly sensitive and specific, more recent data questioned the specificity of TLE1 as it may be positive in other neoplasms, including tumours in the histological differential diagnosis of SS; for example up to 30% of MPNST, 8% of SFT and 69% of malignant mesotheliomas (2; 8; 9). Accordingly when pathologists are faced with a TLE1 positive tumour for which the morphological differential diagnosis includes SS, it may still be necessary to perform molecular studies to establish the presence of a diagnostic t(X;18)

translocation. TLE1 positivity in non-SSs has only been described in non-epithelial malignancies and predominantly in mesenchymal tumours. In our practice we have occasionally encountered TLE1 positive non-mesenchymal tumours (where the initial differential diagnosis included SS) which prompted further molecular studies to exclude the presence of a t(X;18) translocation. We anticipate that TLE1 positivity can occur in epithelial malignancies, tumours that can be difficult to distinguish from SS and this may be more frequent than is currently appreciated. In an era of greater fiscal constraints, it is important to highlight this to avoid overuse of more expensive molecular studies. To this end we propose to investigate TLE1 staining further in epithelial neoplasms using a variety of TMAs.

Reference:	**NIB15-0176**
Chief Investigator:	**Turkington, Richard**
Title:	**Molecular epidemiology biomarkers and oesophageal cancer prognosis**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**25/05/2016**

Summary

The prognostic role of immunohistochemical biomarkers that are related to, and can be modified by, factors such as medication use, nutritional status and other lifestyle habits remains understudied in general and particularly for oesophageal cancer. The aim of the proposed molecular epidemiology research is to investigate a variety of immunohistochemical markers that are related to modifiable risk factors and to explore their role in oesophageal cancer progression (recurrence-free survival) and survival (cancer-specific and all-cause mortality). The objectives are to investigate the association between oesophageal cancer prognosis and: 1. Vitamin D receptor expression Vitamin D has been shown to have several generic anti-carcinogenic effects however its role in oesophageal cancer is controversial and may actually confer poorer outcomes when vitamin D levels are sufficient. Vitamin D exerts its biological effects by binding to the vitamin D receptor (VDR). 2. Beta-adrenergic receptor expression Beta-adrenergic receptor can be modified by use of beta-blocker medications, which have been predicted to influence survival in several cancer sites including breast, melanoma, colorectal and prostate cancer. 3. COX-2 expression COX-2 expression may be an effect modifier of aspirin use in the chemoprevention of cancers, as has been evidenced for colon cancer. Randomised controlled trials are underway for aspirin use and oesophageal cancer risk but the role of aspirin in progression is still unclear. Understanding the association between COX-2 expression and oesophageal cancer progression could guide future stratified medicine trials in this area. 4. Oestrogen and androgen receptor expression Oesophageal cancer predominantly affects males and the role of sex hormones in prognosis remains unclear. Methods Chemotherapy- and surgically-treated oesophageal cancer specimens and data have been collected as part of previous projects (NIB12-0032 and NIB12-0062). To date, n=156 cancer resections have been collated, of which 87 relapses have occurred. Immunohistochemical analysis will be conducted within the NI-Molecular Pathology Laboratory at Queens University Belfast, where all markers of interest have been validated to investigate their association with other tumour sites (eg. colon, breast). Cox proportional hazards analysis will investigate the association between immunohistochemical markers relation to oesophageal cancer progression. Significance of results that may be obtained Findings from this research will provide insight into novel, modifiable, mechanisms involved in oesophageal cancer progression. The study may therefore provide new opportunities for the secondary prevention of, and improved survival from, oesophageal cancer.

Reference:	**NIB15-0185**
Chief Investigator:	**Richard Kennedy**
Title:	**Investigating gene methylation as a prognostic biomarker of Prostate Cancer**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**16/02/2016**

Summary

Prostate cancer is diagnosed in approximately 40,000 patients per year in the UK of which the majority present with potentially curable disease. Curable patients can either be treated with radical resection of the prostate or radical radiotherapy. Despite this 20% of patients receiving radical therapies develop disease recurrence and may benefit from additional adjuvant treatment such as more extensive radiotherapy or adjuvant hormonal therapy. In addition, there is a population of prostate cancer patients whose primary disease will remain indolent and may not require radical treatment. At present, treatment decisions are based on the Gleason score, which is a relatively weak prognostic factor. Our research group has therefore focused on understanding the biology underlying the progression to metastatic disease in poor outcome primary prostate cancers with an aim to developing prognostic assays and novel targeted therapeutic strategies. Specifically in the first instance we wish to identify those men at risk of disease recurrence following radical prostatectomy surgery. We have gene expression data which shows a high number of down-regulated genes in the metastatic biology subgroup. Importantly, this genetic subgroup predicts poor outcome independent of known prognostic factors such as Gleason score and had performance independent of clinical prognostic factors in multivariate analysis. The identification of patients at high risk of recurrence following surgery is a key clinical requirement to identify those men that should have received adjuvant chemotherapy or radiation treatment while sparing those that do not require such interventions and the associated toxicities. At a molecular level, the group was defined predominantly by loss of gene expression. Of these underexpressed genes, the vast majority have been correlated with increased methylation status. This study will have two separate arms investigating the utility of methylation status for prostate cancer prognosis. Initially, we wish to investigate the methylation status of resections compared to that of matched biopsies, confirming that methylation status is reflective of gene expression data and is equivalent between resection and biopsy. Secondly, we aim to translate a methylation assay to cell free DNA (cfDNA) obtained from plasma samples of Prostate Cancer patients. This will allow for a liquid biopsy negating the need for resection and/or invasive biopsy for the prognosis of Prostate Cancer. Current research indicates methylation status of genes to be reflected in cfDNA much more readily than gene expression i.e. RNA or gene mutation status, therefore highlighting the benefit of this approach. The gene signature and methylation pattern we intend to study is prognostic and will be of most benefit to those patients with gleason score 7 who are deemed intermediate with no further stratification for treatment decision making, although some would benefit from more aggressive treatment whereas others would not. Our signature stratifies approximately 35% of patients into a poor prognostic group, therefore to obtain sufficient numbers and keep the powering of the original study we need to ask for 60 x gleason 7 matched biopsy and resection. As controls, we need to compare these gleason 7s to 10 x low grade matched biopsy and resection and 10 x high grade biopsy (and resection where possible).

Reference: **NIB15-0188**
Chief Investigator: **Richard Kennedy**
Title: **A study investigating the use of DDRD as a predictive biomarker for Cisplatin based chemotherapy response in Non-small cell lung cancer**
Sponsor: **Queen's University Belfast**
Location of Research: **Centre for Cancer Research & Cell Biology**
Date of Approval: **16/02/2016**
Summary

Non-small cell lung cancer (NSCLC) is the second most common malignancy among men and third among women in the UK. In the UK, patients with early stage NSCLC are offered adjuvant cisplatin-based therapy (ACT) post-surgery. However, ACT only confers a 4-15% 5-year survival advantage with some significant associated toxicity. There is therefore a need for strategies to identify the specific patients who benefit from this treatment. We have developed a 44-transcript DNA microarray assay, the DNA damage repair deficient (DDRD) assay. This assay identifies a molecular subgroup of cancers that have lost the DNA damage response FA/BRCA pathway, resulting in sensitivity to DNA damaging chemotherapeutic agents such as cisplatin. It is estimated that this pathway is deficient in 25% of all solid tumours through mutation or epigenetic silencing of key components. The DDRD assay has been shown to predict response to neoadjuvant FEC chemotherapy in 203 breast cancer patients (odd ratio 4.01) and predicts a superior outcome following adjuvant chemotherapy in 114 node negative patients (hazard ratio 0.27). Loss of the FA/BRCA pathway has been reported in up to 44% of NSCLC. We therefore applied the DDRD assay to a published dataset of 133 early stage lung cancers treated with adjuvant cisplatin-based therapy or observation and found that the DDRD molecular subgroup comprised 25% of this disease. 25% of patients classified as being within the DDRD subgroup had a survival benefit following adjuvant cisplatin-based therapy (hazard ratio 5.01 p=0.032) compared to those outside the group (hazard ratio 1.43 p=0.414). The aims of this study are 1) Establish a clinico-pathological database from 114 NSCLC patients from the Belfast trust 2) Provide further evidence that the DDRD assay is predictive in identifying those patients who will respond to ACT.

Reference: **NIB15-0189**
Chief Investigator: **Mills, Ian**
Title: **Characterization of IRF7 as prostate cancer marker**
Sponsor: **Queen's University Belfast**
Location of Research: **Centre for Cancer Research & Cell Biology**
Date of Approval: **02/02/2016**
Summary

Over a period of several years, 20-30% of diagnosed prostate cancer cases progress to treatment-resistant metastatic disease. In the course of the last five years a number of new therapeutic strategies have been clinically approved for the treatment of metastatic disease, and most have focussed on targeting androgen receptor signalling. Despite this, new therapies in end-stage disease typically confer median survival benefits of around four months. Collectively this implies that the biology of prostate cancer in end-stage is highly stress adaptive. Our goal is to determine how prostate cancer cells adapt to and survive stress. Results: Cancer cells are subjected to both intrinsic (associated with genomic rearrangements, somatic mutations and epigenetic and metabolic) and extrinsic (microenvironmental and therapeutic) stresses. Using PTEN-loss as an example of intrinsic stress and radiation as an example of therapeutic stress we have established that both stresses impact on common pathways in prostate cancer cell lines. These include the expression of markers of EMT (eg. CD44), inflammation (the Type I interferon response) and the unfolded protein response. Our aim now is to identify the drivers for these phenotypic and gene expression changes, and identify therapeutic interventions that can restrict their emergence. A potential mediator is Interferon regulated factor 7 (IRF7), a transcription factor previously linked to stress-induced senescence, is known to regulate the expression of genes within the Type I interferon signature. We are exploring whether IRF7 is required for radiation induced IRGS and whether this is associated with pro-metastatic biologies and radiation resistance. Conclusions:

Insight into the mechanisms of radiation resistance will aid the development of therapeutic strategies to improve radiation therapy for prostate cancer. As radiotherapy resistance in prostate cancer has been shown to be mediated by the tumour microenvironment the impact of interferons on the behaviour of tumour derived fibroblasts will also be explored.

Reference:	**NIB15-0191**
Chief Investigator:	**Richard Kennedy**
Title:	**Validation of the DDRD assay onto RNA-seq platform from FFPE breast tissue**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**20/04/2016**

Summary

In 2007 with support from Invest NI, Almac Diagnostics undertook a programme to identify novel molecular subtypes in key cancers using gene expression analysis of archived tumour samples. The programme was an overwhelming success with 3 key subtype derived biomarkers identified, 1 of these has since been commercialised (DDRD) 1 is undergoing commercialisation (AADx) and 1 is undergoing independent clinical validation (prostate prognostic). In some instances the expression of multiple genes may be required to identify a molecular subtype of clinical interest. In this case a multigene signature on a cDNA-microarray platform such as the Almac DSA technology may be the most appropriate delivery technology for the biomarker. However, it may be apparent that a molecular subtype of interest is largely defined by a specific gene mutation(s), or transcript variants in those genes. In this case Next Generation Sequencing (NGS) may be the most suitable platform. Therefore we aim to analyse the mutational pattern of tumours by investigating and defining a robust method to allow transfer of the DDRD and AADx subtype profiles onto RNA-Seq analysis from FFPE material. The advantages of RNA-Seq are considerable including assessment of gene expression plus mutational analysis at the same time, the detection is not biased by the design of the array based upon assumptions about the transcriptome and identification of fusion transcripts caused by genomic re-arrangements not detectable by array. Once we have successfully proven that the transferred assay is precise for a panel of embedded cell line material and a random selection of FFPE clinical material from a tissue vendor, we wish to validate the test independently in a cohort of breast FFPE samples previously used for the validation of the original DDRD microarray platform.

Reference:	**NIB16-0194**
Chief Investigator:	**Vicky Coyle**
Title:	**Characterisation of exceptional responders to systemic therapy for advanced melanoma**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**26/05/2016**

Summary

Both spontaneous regression of melanoma and complete or durable responses to treatment for advanced disease are well recognised. If uncommon occurrences, however the underlying biology of this unique subgroup is not well characterised. While attempts have been made to identify markers predictive of response to various systemic therapies or prognosis the focus has also been on predicting response or outcome in general terms rather than investigating the unique subgroup of patients who are exceptional responders to treatment. The available evidence does suggest that there are distinct molecular characteristics of the tumour and its microenvironment associated with exceptional (either complete and/or durable) response to systemic therapy however these are yet to be fully described or elucidated. This study will use transcriptional profiling and mutational analysis to characterise a cohort of exceptional responders to provide novel insights into the biology of this uncommon but well recognised subgroup.

Reference:	**NIB16-0198**
Chief Investigator:	**Peters, Christopher**
Title:	**Validation of Prognostic Index containing both clinical and molecular features to predict outcome in Oesophageal Adenocarcinoma**
Sponsor:	**Imperial College London**
Location of Research:	**Department of Academic Surgery, St Mary's Hospital**
Date of Approval:	**25/05/2016**

Summary

Whilst there have been many molecular prognostic signatures published very few have achieved widespread clinical adoption. In particular prognostic signatures in cancer have rarely been prospectively validated or combined with clinical staging in a way that makes them clinically useful. This research project aims to combine a previous created and retrospectively validated three-gene prognostic signature for oesophageal adenocarcinoma with classical clinical staging to create a prognostic index scoring system. This will allow stratification of patients into groups with significant differences in outcome and also enable predictions to be made as to the likelihood of survival. The three-gene signature has already been retrospectively validated and a prognostic index created consisting of both the molecular features of a tumour and its classical staging. This collaboration will apply this prognostic index to the Northern Ireland Cohort. This will assess the ease with which it can be applied but also its clinical utility both in terms of stratifying patients and predicting outcome. The objective is to retrospectively validate a prognostic index for oesophageal adenocarcinoma incorporating both clinical and molecular features. This project is the stepping-stone towards a larger prospective study assessing the Prognostic Index's value in making management decisions. This is a truly translational research project that will begin the process of turning an interesting molecular finding into a tool that can improve the management of patients with this increasingly common cancer with notably poor outcomes.

Reference:	**NIB16-0199**
Chief Investigator:	**Karen Keating**
Title:	**Optimisation and validation of a predictive gene expression assay in high grade serous ovarian cancer biopsy samples**
Sponsor:	**Almac Diagnostics**
Location of Research:	**19 Seagoe Industrial Estate, Craigavon**
Date of Approval:	**02/06/2016**

Summary

The objective of this research study is to identify the predictive utility of a 63-gene microarray signature (the AADx gene signature) for use as a diagnostic test to predict the clinical outcome of high grade serous ovarian cancer (HGSOC) patients following treatment with chemotherapy using archived formalin fixed paraffin embedded (FFPE) biopsy tissue. The biopsy based assay will then be analytically validated for use as a diagnostic assay in the HGSOC setting, similar to the resection based assay previously developed at Almac. This assay will enable stratification of patients with HGSOC for treatment with either chemotherapy or more targeted drugs such as an anti-angiogenic agent. One future use of the biopsy based assay is clinical trial enrichment in an early phase clinical trial to evaluate a novel anti-angiogenic therapeutic. Almac are initially requesting access to 10 biopsy samples to assess feasibility.

Reference:	**NIB16-0200**
Chief Investigator:	**Richard Kennedy**
Title:	**Investigation of methods for the detection of tumour derived mutations in cfDNA**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**26/05/2016**

Summary

We wish to investigate a range of methods for the detection mutations in cell-free DNA (cfDNA) including NGS and digital PCR alongside enrichment methods such as exosome isolation, targeted amplicon sequencing and COLD PCR. NGS and digital PCR, particularly droplet digital PCR (ddPCR) are emerging technologies in the analysis of cfDNA. NGS offers larger amounts of base pair information but much work needs to be done to improve the sensitivity particularly with reference to cfDNA. The fragmented nature of cfDNA makes NGS analysis more challenging; in addition the cost and analysis involved in whole genome sequencing makes it less attractive for a diagnostic approach. We wish to develop a targeted NGS panel, where only select commonly mutated genes or regions of commonly mutated genes are sequenced cutting down on processing costs and the amount of information to be analysed. ddPCR, on the other hand offers high sensitivity but information is limited the specific assay performed. Studies have reported the detection of mutations as low as 0.05% with ddPCR compared to 3-5% for NGS. A potential approach to overcome the limitations of both NGS and ddPCR would be to combine the two, using NGS for mutation discovery and ddPCR for the monitoring of that specific mutation during treatment. Our focus in the original project was PI3K mutations, we will therefore initially focus on PI3K mutations in this new project but the technologies we will be investigating as well as the techniques we will develop will allow for the investigation of many more mutations relevant to the detection and treatment of breast cancer.

Reference:	**NIB16-0203**
Chief Investigator:	**Paul Mullan**
Title:	**The development of early warning diagnostic and treatment response markers of Non-Uterine Pelvic High Grade Serous Carcinomas**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**09/09/2016**

Summary

High Grade Serous Carcinomas (HGSCs) constitute the most common type of gynaecological cancer and differ from Low Grade Serous Carcinomas (LGSCs) in underlying pathogenesis, molecular events, behaviour and prognosis. HGSC has a worse prognosis compared to LGSC and is usually detected as stage 3 or 4 metastatic disease. HGSCs strongly associate with defects in the familial breast/ovarian cancer genes BRCA1 and BRCA2 and show an exceedingly high rate of p53 mutations (>95%). There is increasing evidence to suggest that HGSCs actually arise from the distal fallopian tube (FT) with the proposed precursor lesion being serous tubal intraepithelial carcinoma (STIC). We have demonstrated through microarray profiling and unsupervised clustering analyses that highly similar biology exists between STIC and matched HGSCs, compared to matched ovarian surface epithelium samples, confirming this hypothesis. Indeed, methylation arrays performed on the same cases show that there are also methylation events occurring in early disease (STIC) which are maintained or increased in the resultant HGSCs. We believe that early detection of HGSCs would be of great importance in helping to improve the overall treatment of this disease, in particular for high-risk (BRCA1/BRCA2) carriers. Currently BRCA carriers have very limited options for disease management and many elect to undergo prophylactic surgeries upon completion of their families, often in their mid-thirties/early-forties. Using differential genelists from our microarray experiments we have identified and validated (RqPCR both in cell lines and primary tissue and ELISA in sera) a number of secreted protein markers show promising

differentials between non-cancer control and HGSC patients. We will further validate secreted protein markers and develop assays to measure methylation of genomic regions, allowing us to also measure differential methylation events occurring in circulating tumour DNA in sera. These combined early warning biomarkers could represent useful tools in the clinical management of HGSC in high-risk women.

Reference:	**NIB16-0204**
Chief Investigator:	**Stuart McIntosh**
Title:	**Breast cancer initiating events in BRCA mutation carriers - an exploratory pilot study**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**02/06/2016**

Summary

BRCA mutation carriers at are a high lifetime risk of developing breast cancer, but currently no effective chemopreventive strategies exist to reduce the breast cancer risk for these women. The mechanisms by which tumours develop within the breasts of BRCA mutation carriers are not well understood, although BRCA loss of heterozygosity and PTEN and TP53 mutations have been implicated in the development of cancers. In normal sun-exposed human skin, multiple areas carrying a significant somatic mutational burden have been identified, many of which are key drivers of cutaneous squamous cell carcinomas. Our preclinical data suggests that exposure of breast cells to oestrogen and its metabolites may have an analagous, DNA-damaging effect. The identification of consistent early mutational events within the unaffected breasts of BRCA mutation carriers may reveal targetable lesions which could be exploited for chemopreventive or diagnostic purposes. We therefore propose to explore the mutational landscape in the unaffected breast of BRCA mutation carriers using two approaches: 1. evaluation of multiple areas of the breasts in women who carry BRCA mutations who have undergone risk-reducing mastectomies, using immunohistochemistry to establish the existence of areas of TP53 and PTEN overexpression/silencing, and for BRCA LOH using FISH in retrospective FFPE samples. 2. Carry out whole exome sequencing using fresh tissue from multiple areas of unaffected breasts from BRCA mutation carriers collected prospectively during routine risk-reducing surgery.

Reference:	**NIB16-0207**
Chief Investigator:	**Steven Walker**
Title:	**Technical migration of the DDRD assay from resection sample material to core biopsy sample material in breast cancer**
Sponsor:	**Almac Diagnostics**
Location of Research:	**19 Seagoe Industrial Estate, Craigavon**
Date of Approval:	**02/11/2016**

Summary

Almac Diagnostics have developed a molecular assay in breast cancer that can identify those patients that are most likely to benefit from standard of care anthracycline-based chemotherapy, namely the DDRD Assay. This performance has been validated in a publicly available independent cohort of 203 patients. The DDRD Assay predicted complete pathologic response vs residual disease after neoadjuvant DNA-damaging chemotherapy (5-fluorouracil, anthracycline, and cyclophosphamide) with an odds ratio of 3.96 (95% confidence interval [CI] =1.67 to 9.41; P = .002). An independent cohort of 191 breast cancer patients treated with adjuvant 5-fluorouracil, epirubicin, and cyclophosphamide were profiled at Almac using the DDRD Assay. A DDRD positive test result predicted 5-year relapse-free survival with a hazard ratio of 0.37 (95% CI = 0.15 to 0.88; P = .03) compared with the assay negative population (Mulligan et al 2014, J Natl Cancer Inst: 106(1)). As breast cancer is a heterogeneous disease and considering the DDRD assay is a gene expression based assay, tissue heterogeneity or technical differences between biopsy and resection techniques may impact DDRD scoring in these tissue sample types. This may be due to differences in percentage viable cell content, tumour content,

presence of tumour infiltrating lymphocytes, etc. As previous data for the DDRD assay in breast cancer has been generated from resection material, the objective of this study is to technically migrate the DDRD signature threshold from resection to core biopsy material and to determine if DDRD signature scores are comparable between both sample types in a cohort of breast cancer patients from whom paired biopsy/resection samples are available.

Reference:	**NIB16-0210**
Chief Investigator:	**Richard Turkington**
Title:	**Investigation of Axl and FGFR3 as a poor prognostic factor in oesophageal adenocarcinoma (OAC)**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**11/08/2016**

Summary

Oesophageal cancer is the sixth most common cause of cancer death and accounts for around 5% of all cancer deaths in the UK. The incidence of oesophageal adenocarcinoma (OAC) in men in the UK has risen 50% in the last 25 years. Neo-adjuvant therapy confers a significant improvement in survival but the optimal approach for individual patients remains unclear. Axl is a member of the TAM (Tyro, Axl, Mer) family of receptor tyrosine kinases (RTK) and has been shown to be overexpressed in a variety of human cancers with a role in tumour progression and metastases. Upregulation of Axl has been identified as poor prognostic marker and a key mediator of cancer cell migration and invasion in colorectal cancer. Fibroblast growth factor receptor 3 (FGFR3) is a part of a family of four fibroblast growth factor receptors that share similar structures and functions. FGFR3 has shown to be overexpressed in approximately 50% of both invasive and non-invasive bladder cancer cases. Having obtained promising preliminary data we wish to investigate the role of Axl and FGFR3 as a poor prognostic factor in oesophageal adenocarcinoma. Materials and Methods Chemotherapy- and surgically-treated oesophageal cancer specimens and data have been collected as part of previous projects (NIB12-0032 and NIB12-0062). To date, n=156 cancer resections have been collated, of which 87 relapses have occurred. Immunohistochemical analysis will be conducted within the NI-Molecular Pathology Laboratory at Queen's University Belfast, where all markers of interest have been validated to investigate their association with other tumour sites (eg. colon, breast). Cox proportional hazards analysis will investigate the association between immunohistochemical markers relation to oesophageal cancer progression. Results Our preliminary data indicates increased activation of the receptor tyrosine kinases Axl and FGFR3 in an oesophageal adenocarcinoma cell line (OE33) which has been transformed into a resistant cell line following repeated exposure to the allosteric AKT inhibitor ALM301 (Almac Drug Discovery). Previous data has shown that the OE33 301 resistant cell line is more migratory and invasive in comparison to the parental cell line. We hypothesise that activation of these receptor tyrosine kinases is driving an EMT phenotype and may be a mechanism of acquired resistance to ALM301. We seek to examine the effectiveness of Axl and FGFR3 as markers of adverse prognosis in a cohort of oesophageal adenocarcinoma patients.

Reference:	**NIB16-0211**
Chief Investigator:	**Stuart McIntosh**
Title:	**Real time tissue characterisation using mass spectrometric analysis**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**01/07/2016**

Summary

There are currently no methods which provide real time, in vivo, in situ tissue diagnostics in the operating theatre. It is possible that the oncological nature of breast tissue may be accurately identified using mass spectometric analysis of tissue specific ions released during thermal degradation of tissue as occurs during

electrosurgery. This project aims to develop histologically validated spectral databases for normal, benign and malignant breast tissue using ex vivo tissue analysis by rapid evaporative ionisation mass spectrometry (REIMS). This will consist of a prospective fresh tissue sample collection. Fresh tissue which is not required for diagnostic histopathological evaluation (following assessment by a specialist tissue pathologist) will be used ex vivo for mass spectral analysis. Fresh samples will be transferred to the IGFS where they will be analysed by REIMS. The tissue sections will then be formalin fixed, paraffin embedded, sectioned and stained in such a way that the diathermy burn area (which has been analysed by REIMS) can be subject to histopathological examination, together with the surrounding tissue. This will provide histopathological validation for the REIMS spectra collected. This will be done in close conjunction with surgeons and tissue pathologists, so that it does not interfere with the pathological staging of malignancy.

Reference:	**NIB16-0212**
Chief Investigator:	**Philip Dunne**
Title:	**Mutational-genotype stratification highlights Bcl-xL as a prognostic factor associated with relapse in stage II/III BRAF mutant Colon Cancer (CC)**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**25/07/2016**

Summary

BRAF mutations occur in approximately 8-15% of colon cancer (CC) tumours and have been associated with poor survival in the metastatic setting. Previous studies have undertaken comparative analysis of transcriptional changes between stage II/III BRAFMT and BRAFWT tumours. This analysis was used to identify a subgroup of patients with shorter overall survival after relapse, but importantly it failed to reveal the critical biology which can identify stage II/III patients at higher risk of relapse from within the BRAFMT genotype. Therefore, to elucidate the transcriptional signalling associated specifically with disease relapse in stage II/III BRAFMT tumours, we performed supervised analysis, based on risk of relapse, of transcriptomic datasets within this genotype. Changes in gene expression associated with increased and decreased risk of relapse in the BRAFMT genotype were assessed using transcriptomic data from a large stage II and III CC cohort. This analysis identified transcripts significantly associated with adverse relapse free survival. Of the transcripts identified Bcl-xL was identified as significantly associated with relapse in stage II/III BRAFMT CC patients. High gene expression levels of Bcl-xL, a key regulator of apoptosis, was found to be associated with poor prognosis specifically in BRAFMT tumours (HR=8.3 (95% CI 1.7-41.7) but not in KRASMT/BRAFWT or KRASWT/BRAFWT tumours. This unique finding demonstrates the utility of this stratified analysis approach and also highlights the differences in prognostic biology between BRAFMT and KRASMT tumours. In addition, we confirmed that Bcl-xL mRNA and protein expression is epithelial derived within the overall cellular components of these tumours. These findings provide compelling evidence for the clinical evaluation of the prognostic role of Bcl-xL in the BRAFMT subgroup of stage II/III CC and suggest that Bcl-xL targeted therapies may be efficacious in this otherwise poor prognostic subgroup.

Reference:	**NIB16-0214**
Chief Investigator:	**Kienan Savage**
Title:	**Developing assays to extract protein from FFPE tissue for protein microarrays**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**06/10/2016**

Summary

A great effort has been made into understanding the fundamental mechanisms of cancer pathology. Great advancements in genetic techniques and approaches have elucidated numerous gene targets and pathways

that are implicated in disease progression. Genomic studies have been vital to our understanding and the development of treatment and crucial diagnostic tools but the link between genetic abnormalities and disease onset and progression remains to be fully elucidated. One way of examining this link would be in examining the gene product/ protein. Protein microarrays, both forward phase and reverse phase, are incredibly useful, sensitive and quantitative methods of performing high-throughput screening of proteins and important pathways involved in disease biology. They utilize very small quantities of protein and can examine multiple proteins, or protein states (e.g. phosphorylation state) simultaneously, which is beneficial in the development of diagnostic tools compared to current accepted methods such as western blotting or immunohistochemistry that can be extremely labour intensive and requires much larger quantities of protein. The gold standard for preserving clinical tissue samples, such as resected tumour tissue, is formalin-fixed paraffin-embedded (FFPE) processing. Clinical samples are classically used for histological profiling of the tumour tissue and advancements have been made in extracting DNA and RNA from FFPE tissue, with varying degrees of success. Protein extraction from FFPE tissue has been regarded as difficult or impossible owing to the extensive crosslinking from the formalin preservation process, or antigen masking that has led to problematic immunohistochemistry investigations. Recently studies (Mansour et al 2016, Becker et al 2007, Addis et al 2005) have shown that protein can be extracted from FFPE tissue, following deparaffinization and rehydration steps. This study aims to develop and optimize a protocol for the extraction of whole tissue protein lysates from FFPE tumour tissue, from breast, ovarian and prostate tumour tissue samples. Once a robust, reliable and reproducible method is developed we want to develop this method for use with FPPAs and RPPAs that would facilitate the assessment of protein expression signatures in relevant tumour cohorts, which would in turn allow for the further development of diagnostic tools from this technology.

Reference:	**NIB16-0215**
Chief Investigator:	**Philip Dunne**
Title:	**Defining the landscape of aggressive early-invasive pT1/pT2 colorectal cancer**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**20/10/2016**

Summary

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the Western World. Transcriptional profiling of stage II/III CRC has identified 4 molecular subtypes with prognostic value: Consensus Molecular Subtypes 1-4 (CMS). Additionally, histopathology has identified a number of factors which provide additional prognostic value. Molecular profiling efforts have generated a number of prognostic/predictive transcriptional signatures in the adjuvant disease setting, some of which are used clinically to advise clinical management of stage II/III patients. In contrast to stage II/III CRC, there are limited studies examining the molecular profile of stage I, particularly pT1 tumours, although the applicant's 2015 senior author publication has identified a poor prognostic group through immuno-histochemical biomarker-based stratification in stage I disease. Molecularly profiled cohorts focused on this early stage are rare (only 17 pT1 profiles within The Cancer Genome Atlas, Feb-2016), resulting in limited opportunities to define underlying biology or to either develop or test prognostic/predictive classifiers. Although the majority of early-stage CRC tumours grow slowly and can be clinically managed, there are a small group of patients with aggressive disease who are identified following cancer-related symptoms and are ultimately diagnosed with late-stage disease. Due to bowel screening we will now for the first time begin to identify these same patients with aggressive disease while they are asymptomatic and at a much earlier stage of disease than before. As a result there is now an urgent need to understand the biology of this early-aggressive disease to enable the identification and prioritisation of patients with high molecular risk while they are still clinically manageable. The applicant now proposes to carry out the following in pT1 tissue: Identification of high-risk tumours based on clinical information regarding relapse-risk and overall cancer-specific survival • Pathological assessment of features such as stroma/immune content and epithelial morphology Transcriptional microarray profiling, with

Affymetrix methodology validated in FFPE Tissue-based in situ validation of the applicants published prognostic biology from stage II/III, such as molecular subtypes, immune cell infiltration and drivers of invasion.

Reference:	**NIB16-0217**
Chief Investigator:	**Suneil Jain**
Title:	**How does radiotherapy affect immune signalling and the tumour microenvironment in men with Localised Prostate Cancer?**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**25/08/2016**

Summary

Preliminary data suggests that the immune gene signature discussed above is a potentially valuable prognostic biomarker in prostate cancer. To date all information regarding this signature has been gained from diagnostic biopsies and surgical resection specimens. In order to determine if this immune signature will have a utility in prostate cancer it is important that we establish whether radiotherapy alters the immune gene expression in tumour samples. Studies in breast cancer have illustrated that this signature identifies tumours which are DNA damage repair deficient and therefore, show have increased sensitivity to DNA damaging chemotherapeutics such as platinum based drugs, anthracyclines and targeted agents such as PARP-1 inhibitors, yet to date, no studies have explored response to radiation. Furthermore, it is plausible radiation exposure will induce an intra-tumoural immune reaction with recruitment of lymphocytes to sites of cellular damage. This process may sensitise tumours to immunotherapeutic agents, a hypothesis that could be tested in future clinical trials. 2.1 Primary Objectives 1. To determine if immune gene status is altered by treatment with ADT or radiotherapy in the form of External Beam Radiotherapy (EBRT) or brachytherapy. 2. To determine if lymphocytic infiltration is associated with immune gene status or HIF1α in prostate cancer, and if treatment with both radiotherapy and ADT alters the pattern of infiltration. 3. To determine if the immune gene signature could be utilised as a biomarker to highlight patients who will respond favourably to radiotherapy. 2.2 Secondary Objectives 1. To determine if the immune gene status of a patient has an influence on progression free and overall survival for patients receiving radiotherapy.

Reference:	**NIB16-0218**
Chief Investigator:	**Darragh McArt**
Title:	**Molecular changes between primary and recurrent GBM**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**02/11/2016**

Summary

Glioblastoma (GBM) is the most prevalent and aggressive of malignant primary brain tumours, which remains among the most difficult of cancers to treat. Despite multi-modal therapy, including surgical resection, radiotherapy and chemotherapy (temozolomide), GBM continues to have a very poor prognosis, with a median survival of 12-18 months from the time of diagnosis. The resistance to therapy and ultimate recurrence of GBM is thought to originate from a sub-population of tumour cells residing in the initial tumour, identified as the glioma-initiating or glioma-stem cell (GSC). In an attempt to identify and understand the biology underpinning recurrence in GBM, we have previously used public available data to examine differentially expressed genes contrasting clinically resected primary and recurrent glioblastoma tissue. Using this gene list as a signature of GBM recurrence, we carried out a novel in silico drug screen developed in-house, QUADrATiC, using a subset of FDA approved therapeutic compounds within the LINCS (Library of Integrated Network-based Cellular Signatures) database to select appropriate drug candidates that target therapeutically resistant and recurrent GBM. This work highlights the adaptability and efficacy of the

QUADrATiC connectivity mapping software package for selecting optimal agents for use in a clinical setting, in this case, specifically targeting the GSC sub-populations within this heterogeneous tumour, to reduce therapeutic resistance and tumour recurrence. Although this public data has confirmed different signalling patterns between primary and recurrent tumour tissue, in-depth genomic (e.g. next generation sequencing data) and phenotypic (i.e. clinical, pathology and imaging) characterization of smaller cohorts of patients will enable interrogation of this heterogeneous tumours, to personalize therapy. We have assembled a cohort of 15 patient samples containing primary resection and multiple recurrence tissue samples (n=58 blocks in total). This application proposes to carry out H&E assessment of these samples followed by transcriptomic profiling using methods optimised for small FFPE samples.

Reference:	**NIB16-0222**
Chief Investigator:	**Peter Hamilton**
Title:	**The computerised identification of tumour regions for the purposes of macrodissection**
Sponsor:	**PathXL/Philips Digital Pathology Solutions, Belfast**
Location of Research:	**PathXL/Philips Digital Pathology Solutions, Belfast**
Date of Approval:	**11/11/2016**

Summary

Molecular evaluation of nucleic acid extractions from FFPE material generally requires enrichment of the tumour cell fraction by macrodissection. This normally is carried out by an experienced pathologist who manually annotates the glass slides using a microscope and pen. This is time consuming, expensive, laborious and is subject to inter- and intra-pathologist variation. This study aims to develop a set of computer algorithms, using previously defined methods based on texture extraction and support vector machine classification, that can distinguish tumour from non-tumour tissue within biopsy and resection samples across a range of tumour types; specifically lung, colorectal, breast, prostate, melanoma and ovarian tumours. The algorithm will be generated using whole slide scans and will allow for automated annotation of tumour samples for subsequent macrodissection and an estimation of the % tumour cells within the samples. Primary objectives: To develop algorithms for the automatic identification of lung, colorectal, breast, prostate, ovarian and skin (melanoma) cancer from H&E tissue samples Algorithm development will be carried out on digital images of the glass slides and will be based on pattern analysis of tumour and non-tumour regions of the images To integrate these algorithms within a general delivery framework for molecular pathology laboratories Secondary objectives: To explore wider applications of automated tumour identification in biobanking, TMA analysis, biomarker discovery and personalised medicine

Reference:	**NIB16-0225**
Chief Investigator:	**Stuart McIntosh**
Title:	**Measurement of oestrogen metabolites and DNA adducts in plasma - optimisation study**
Sponsor:	**Queen's University Belfast**
Location of Research:	**Centre for Cancer Research & Cell Biology**
Date of Approval:	**12/01/2017**

Summary

It is known that certain oestrogen metabolites react with DNA and may induce mutations, which can lead to the development of cancer. Previous work in our lab has shown that BRCA1 mutation carrier cells have higher levels of oestrogen metabolites. As a proof of concept study, 'Chemoprevention in BRCA1 mutation carriers' (CIBRAC), will look at the effects of oestrogen suppression therapy in BRCA1 mutation carriers. An exploratory endpoint of this study is to assess the effects of treatment on oestrogen metabolite and DNA adduct levels in breast, plasma and urine samples using Ultra Performance Liquid Chromatography Tandem Mass Spectrometry (UPLC-MS/MS). On order to reliably quantitate the levels of genotoxic oestrogen

metabolites in plasma, we require plasma samples to analyse with UPLC-MS/MS to optimize the protocol and assay performance. Thus far, we have successfully detected oestrogen metabolites in healthy volunteer plasma, but have not been able to quantify these levels due to the low concentrations in this cohort. This study aims to quantify oestrogen metabolite levels in plasma samples of pre-menopausal women who have had oestrogen receptor positive (ER+ve) breast cancer. This cohort is known to have higher levels of circulating oestrogen and oestrogen metabolites compared to women without breast cancer, facilitating assay optimization and quantification at higher, yet still physiological, oestrogen metabolite levels.

Reference:	**NIB16-0230**
Chief Investigator:	**Phil Sloan**
Title:	**Clinical outcomes in acinic cell carcinoma and salivary secretory carcinoma**
Sponsor:	**Newcastle upon Tyne Hospitals NHS Foundation Trust**
Location of Research:	**Department of Cellular Pathology**
Date of Approval:	**07/03/2017**

Summary

The identification of the ETV1-NTK6 fusion protein in a subset of salivary neoplasms showing acinic differentiation has led to the identification of a new tumour entity defined in the forthcoming WHO classification as salivary secretory carcinoma (SC). There is little published information on the biological behaviour and clinical outcomes of SC. Further, it has been claimed that acinic cell carcinoma and SC can be distinguished by use of an immunohistochemical panel for S100 or mammoglobin with DPAS staining. To date around 300 cases of SC have been published and rare examples of aggressive variants with widespread metastatic behaviour have been recorded. In this study we intend to examine a series of acinic cell carcinomas with paired clinical data from three centres (Royal Victoria Infirmary, Newcastle; Royal Victoria Hospital, Belfast and Edinburgh Royal Infirmary, Edinburgh). All cases will be reviewed by a consensus panel of oral pathologists. Then an immunohistochemical panel including SOX10, DOG-1, S100 and mammoglobin will be performed along with DPAS staining on all cases. This will be followed by testing for ETV6 re-arrangement by FISH and ETV6-NTRK3 fusion by RT-PCR. The tumours will then be re-examined by the consensus panel and stratified into SC or conventional acinic cell carcinoma. The biological behaviour and clinical outcomes will then be compared between the two groups.

NIB REFERENCE NUMBER	DATE RECEIVED	CHIEF INVESTIGATOR	TITLE OF PROJECT	INSTITUTION	OUTCOME	SAMPLES/DATA REQUESTED	PROJECT START DATE
NIB14-0109	05/02/2014	McDowell, Andrew	Isolation of the anaerobic bacterium *Propionibacterium acnes* from cancerous prostate tissue	University of Ulster (NI Centre for Stratified Medicine, Clinical Translational Research & Innovation Centre, Londonderry)	APPROVED (application did not progress - pending new application)	Matched prostate cores with aliquots of urine and serum plus associated clinical data	24.06.2015
NIB14-0119	28/04/2014	Van Schaeybroeck, Sandra	Identification of the key drivers of disease progression in colorectal cancer (C/R NIB12-0060)	Centre for Cancer Research & Cell Biology, Queen's University Belfast	CLOSED		
NIB14-0129	27/08/2014	James, Jacqueline	Characterization of Biobank Samples for High Throughput Analyses	Centre for Cancer Research & Cell Biology, Queen's University Belfast	CLOSED		
NIB14-0141	29/10/2015	Fagnani, Roberto	Evaluation of expression of FOXC1 biomarker in breast cancer samples	3N Diagnostics Ltd Unit 2C, Antrim Technology Park Antrim	CLOSED		
NIB15-0146	08/01/2015	Anderson, Lesley	Infectious agents in progression from Barrett's Oesophagus to Oesophageal Adenocarcinoma. A nested case control within the Northern Ireland Barrett's register	Centre for Public Health, Queen's University Belfast	APPROVED PENDING appropriate MTAs	270 formalin fixed and paraffin embedded Barrett's oesophagus samples (2:1 ratio of those that have not versus those that have progressed to adenocarcinoma) as determined through the NI Barrett's Register	
NIB15-0157	20/04/2015	Kelly, Paul	Molecular aspects of aberrant negative and wildtype p53 staining in Barrett's dysplasia: a pilot study	Histopathology, Belfast Health & Social Care Trust	PENDING		

NIB15-0160	**29/06/2016**	**Flannery, Thomas**	**Investigation of biomarkers and molecular signatures that correlate with therapeutic resistance and recurrence in malignant brain tumours**	**Neurosurgery, BHSCT**	**Provisional Acceptance PENDING**	**200 FFPE malignant brain tumour samples + associated clinical data**	
NIB15-0161	**26/05/2015**	**Salto-Tellez, Manuel**	**Roche Multi-gene and cell-free DNA testing Kits**	**CCRCB, QUB**	**CLOSED**		
NIB15-0166	**23/07/2015**	**McDade, Simon**	**Characterizing p53 family, co-factors, targets and de-regulation in p53 mutated cancers**	**CCRCB, QUB**	**APPROVED – pending completion of MTA**	**1 x H & E and 10 x 5 µm sections for DNA & RNA extraction from up to 40 patient samples**	**22/03/2017**
NIB15-0170	**20/07/2015**	**Mills, Ken**	**Impact of ISS and its constituents on action of thalidomide in myeloma**	**CCRCB/School of Pharmacy, QUB**	**CLOSED**		
NIB15-0171	**30/07/2015**	**Lawler, Mark**	**Stromal derived PDL1 is associated with high levels of immune infiltrate and MSI in early stage CRC**	**CCRCB/QUB**	**CLOSED**		
NIB15-0172	**07/08/2015**	**Irwin, Chris**	**Role of SDF-1 in stromal-tumour interactions in oral cancer**	**School of Dentistry, QUB**	**CLOSED**		

NIB15-0173	**05/08/2015**	**Turkington, Richard**	**Investigation of the DNA Damage Response Deficiency (DDRD) Assay as a Prognostic Biomarker in Oesophageal Adenocarcinoma**	**CCRCB, QUB**	**Provisional acceptance (HSC R & D Doctoral Fellowship funding in place). Work on *the samples to be carried out at Almac Diagnostics under a collaborative agreement; NIB will require sight of agreement before release of samples***	**1 x H & E and 5 x 10 µM sections from each representative tumour block of 194 FFPE cases of oesophageal adenocarcinoma** **Associated clinical data including age, gender, preoperative clinical staging, pathological staging including T/N stage, grade, margins, survival outcomes including relapse-free and overall survival**	
NIB15-0174	**12/08/2015**	**Lawler, Mark**	**Generation of patient derived cell line models**	**CCRCB, QUB**	**PENDING**		
NIB15-0175	**18/08/2015**	**Kelly, Paul**	**Expression of TLE-1 in non-mesenchymal neoplasms. A TMA-based study**	**Histopathology, Belfast Health & Social Care Trust**	**APPROVED**	**Sections from TMAs of appropriate epithelial malignancies held within the NIB (2 sections from each).**	**10/12/2015**
NIB15-0176	**26/08/2015**	**Turkington, Richard**	**Molecular epidemiology biomarkers and oesophageal cancer prognosis**	**CCRCB, QUB**	**APPROVED**	**7 x 3 µm sections from each of 9 oesophageal TMA blocks (63 in total)**	**25/05/2017**

NIB15-0178	**15/09/2015**	**Goodman, Brian**	**Evaluating Tumor Samples for the Cancer Microbiome**	**Evelo Therapeutics, Massachusetts, USA**	**CLOSED**		
NIB15-0184	**22/10/2015**	**McIntosh, Stuart**	**A population-based study of contralateral breast cancer in Northern Ireland**	**CCRCB, QUB**	**BIOBANK IS FACILITATING SAMPLE RETRIEVAL FOR A BELFAST TRUST APPROVED PROJECT**	**Retrieval of slides to facilitate recall of historical FFPE tumour blocks (400 – 500 samples)**	**Awaiting copy of BHSCT MTA**
NIB15-0185	**22/10/2015**	**Kennedy, Richard**	**Investigating gene methylation as a prognostic biomarker of Prostate Cancer**	**CCRCB, QUB**	**APPROVED**	**H & E and 10 x µm sections (for RNA extraction) from 160 prostate tissue samples plus 3 x 10 µm from 19 prostate biopsy blocks**	**16/02/2016**
NIB15-0188	**03/11/2015**	**Kennedy, Richard**	**A study investigating the use of DDRD as a predictive biomarker for Cisplatin based chemotherapy response in Non-small cell lung cancer**	**CCRCB, QUB**	**APPROVED**	**H&E and 2x10 µm sections for RNA extractions from 120 NSCLC tissue samples**	**16/02/2016**
NIB15-0189	**03/11/2015**	**Mills, Ian**	**Characterization of IRF7 as prostate cancer marker**	**CCRCB, QUB**	**APPROVED**	**12 sections from selected control material for IFR7 validation 1 section from each of 3 prostate TMA sections for test IFR7 IHC 1 section from each of 10 biopsies for IFR7 IHC**	**02/02/2016**

NIB15-0191	**02/12/2015**	**Kennedy, Richard**	**Validation of the DDRD assay onto RNA-seq platform from FFPE breast tissue**	**Almac Diagnostics**	**APPROVED –**	**H&E + 10 µm sections from 35 DDRD positive Breast FFPE H&E + 10 µm sections from 35 DDRD negative Breast FFPE**	**20/04/2016**
NIB16-0193	**04/03/2016**	**Richard, Derek**	**Characterising the role of Exosc4 in ovarian tumorigenesis: a prospective anticancer target**	**Queensland University of Technology, Australia**	**CLOSED Researcher did not respond to queries raised by reviewers**		
NIB16-0194	**18/01/2016**	**Coyle, Vicky**	**Characterisation of exceptional responders to systemic therapy for advanced melanoma**	**CCRCB, QUB**	**APPROVED**	**10 FFPE melanomas**	**26/05/2016**
NIB16-0195	**02/02/2016**	**Turkington, Richard**	**Molecular subtyping and Predictive Biomarker Development in Pancreatic Adenocarcinoma**	**CCRCB, QUB**	**PENDING OUTCOME OF A GRANT APPLICATION**		
NIB16-0196	**07/03/2016**	**Furlong, Fiona**	**Medications, Tumor Markers, and Ovarian Cancer Survival**	**School of Pharmacy, QUB**	**LETTER OF SUPPORT FOR GRANT APPLICATION PROVIDED**		
NIB16-0197	**16/02/2016**	**McCulla, Andrea**	**Analytical verification of a TP53 NGS assay in haematological disorders**	**Almac Diagnostics**	**APPLICATION ON HOLD (AT RESEARCHER'S REQUEST)**		
NIB16-0198	**16/02/2016**	**Peters, Christopher**	**Validation of Prognostic Index containing both clinical and molecular features to predict outcome in Oesophageal Adenocarcinoma**	**Department of Academic Surgery Imperial College London**	**APPROVED-PENDING MTA**	**4 sections from each of 7 Oesophageal TMAs plus associated clinical data**	

NIB16-0199	**14/03/2016**	**Keating, Karen**	**Optimisation and validation of a predictive gene expression assay in high grade serous ovarian cancer biopsy samples**	**Almac Diagnostics**	**APPROVED**	**H & E Sections + up to 10 x10 µM sections (where feasible & governed by clinical requirements) from 10 ovarian biopsy FFPE samples**	**2/06/2016**
NIB16-0200	**21/03/2016**	**Kennedy, Richard**	**Investigation of methods for the detection of tumour derived mutations in cfDNA**	**CCRCB, QUB**	**APPROVED**	**53 aliquots of plasma**	**26/05/2016**
NIB16-0201		**Taggart, Cliff**	**Application incomplete**		**CLOSED**		
NIB16-0202		**Conway, Caroline**	**An investigation of molecular markers of prognosis in potentially malignant disorders of the upper respiratory tract.**		**PENDING**		
NIB16-0203	**21/03/2016**	**Mullan, Paul**	**The development of early warning diagnostic and treatment response markers of Non-Uterine Pelvic High Grade Serous Carcinomas**	**CCRCB, QUB**	**APPROVED**	**50 cases FFPE High Grade Serous Carcinoma of the ovary (with matched FFPE STIC lesions, FFPE normal fallopian tube tissue, matched sera) 50 cases FFPE non-neoplastic gynae (with matched sera samples) 10 samples of matched ascites with longitudinally collected sera**	**09/09/2016**

NIB16-0204	**23/03/2016**	**McIntosh, Stuart**	**Breast cancer initiating events in BRCA mutation carriers - an exploratory pilot study**	**CCRCB, QUB**	**APPROVED**	**Samples from cases of normal unaffected breast tissue (BRCA1 and BRCA2 mutation carriers who have undergone bilateral risk reducing mastectomies. Samples from cases of non-BRCA carriers undergoing bilateral breast reduction. 25 x FFPE from NHS Archive (normal breast) fresh frozen tissue samples (10 cases) 10 x 0.5 ml whole blood (10 cases)**	**02/06/2016**
NIB16-0205	**20/05/2016**	**Walker, Steven**	**Retrospective validation of the DDRD assay in a cohort of breast cancer patients treated with neoadjuvant chemotherapy**	**Almac Diagnostics**	**PENDING**		
NIB16-0206			**APPLICATION INCOMPLETE**		**CLOSED**		
NIB16-0207	**05/06/2016**	**Walker, Steven**	**Technical migration of the DDRD assay from resection sample material to core biopsy sample material in breast cancer**	**Almac Diagnostics**	**APPROVED – SAMLES PENDING**	**Sections of representative biopsy and resection from up to 80 cases of locally advanced or inflammatory breast cancer**	**02/11/2016**

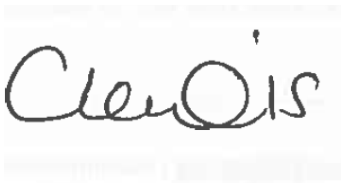
NIB16-0208	**11/05/2016**	**Murray, Liam**	**The International Molecular PAthology Epidemiology ConsorTium (IMPACT: BELFAST COMPONENT)**	**Centre for Public Health, QUB**	**Letter of support provided for grant application**		
NIB16-0209	**13/06/2016**	**Walker, Steven**	**The investigation of the utility of the Almac Diagnostic assays (DDRD & EMT) as a molecular biomarkers for immune checkpoint inhibitor treatment in melanoma**	**Almac Diagnostics**	**PENDING (awaiting response to reviewers' comments)**		
NIB16-0210	**23/05/2016**	**Turkington, Richard**	**Investigation of Axl and FGFR3 as a poor prognostic factor in oesophageal adenocarcinoma (OAC)**	**CCRCB, QUB**	**APPROVED**	**2 x 3 µm sections from each of 7 oesophageal TMA blocks (14 in total)**	**11/08/2016**
NIB16-0211	**02/06/2016**	**McIntosh, Stuart**	**Real time tissue characterisation using mass spectrometric analysis**	**CCRCB, QUB**	**APPROVED**	**50 fresh samples of breast tissue (tumour & normal parenchyma)**	**01/07/2016**
NIB16-0212	**14/06/2016**	**Dunne, Philip**	**Mutational-genotype stratification highlights Bcl-xL as a prognostic factor associated with relapse in stage II/III BRAF mutant Colon Cancer (CC)**	**CCRCB, QUB**	**APPROVED**	**1 x 4 µm section from each of 28 colorectal cancer TMA blocks (NIB13-0069 cohort)**	**25/07/2016**
NIB16-0213	**17/06/2016**	**Murray, Liam**	**Population based studies of risk factors, biomarkers, medications and lifestyle interventions to prevent cancer and improve outcomes in patients with Barrett's oesophagus**	**Centre for Public Health, QUB**	**Letter of support provided for grant application**		

NIB16-0214	**20/07/2016**	**Savage, Kienan**	**Developing assays to extract protein from FFPE tissue for protein microarrays**	**CCRCB, QUB**	**APPROVED**	**30 x 5 µm sections from each of 3 X FFPE tumour blocks (1 breast, 1 ovarian, 1 prostate and all with greater than 50% tumour content)**	**6/10/2016**
NIB16-0215	**22/08/2016**	**Dunne, Philip**	**Defining the landscape of aggressive early-invasive pT1/pT2 colorectal cancer**	**CCRCB, QUB**	**APPROVED**	**10 x 5µm sections from Colorectal Cancer FFPE tissue blocks (39 cases)**	**20/10/2016**
NIB16-0216		**Nemeth Z**	**APPLICATION INCOMPLETE**				
NIB16-0217	**17/08/2016**	**Jain, Suneil**	**How does radiotherapy affect immune signalling and the tumour microenvironment in men with Localised Prostate Cancer?**	**CCRCB, QUB**	**APPROVED**	**H&E + 5 x 10micron sections from prospectively collected FFPE prostate biopsies (200 cases) 200 FFPE (matched diagnostic prostate biopsies) from NHS archive**	**25/08/2016**
NIB16-0218	**09/09/2016**	**McArt, Darragh**	**Molecular changes between primary and recurrent GBM**	**CCRCB, QUB**	**APPROVED**	**6 x 5µm sections from Glioblastoma FFPE tissue blocks (58 blocks from 15 cases)**	**02/11/2016**
NIB16-0219			**APPLICATION INCOMPLETE**		**CLOSED**		
NIB16-0220			**APPLICATION INCOMPLETE**		**CLOSED**		

NIB16-0221	**05/10/2016**	**Stebbing, Justin**	**Molecular basis of breast cancer in pregnancy**	**Imperial College London**	**REJECTED**		
NIB16-0222	**12/10/2016**	**Hamilton, Peter**	**The computerised identification of tumour regions for the purposes of macrodissection**	**PathXL/Phillips Digital Pathology Solutions, Belfast**	**APPROVED**	**Up to 1,000 glass slides from each of the following tumour types: Lung, colorectal, breast, prostate, ovarian and skin cancer Up to 1,000 digital whole slide images from each of the following tumour types: Lung, colorectal, breast, prostate, ovarian and skin cancer**	**11/11/2016**
NIB16-0223	**11/11/2016**	**Kennedy, Richard**	**Investigating the DDRD assay in High Grade Serous Ovarian Cancer**	**CCRCB, QUB**	**PENDING**		
NIB16-0224		**McKenna, Declan**	**APPLICATION INCOMPLETE**	**University of Ulster**			
NIB16-0225	**21/11/2016**	**McIntosh, Stuart**	**Measurement of oestrogen metabolites and DNA adducts in plasma – optimisation study**	**CCRCB, QUB**	**APPROVED**	**1 ml plasma from each of 10 donors with pre-menopausal oestrogen receptor breast cancer**	**12/01/2017**
NIB16-0226	**09/02/2017**	**Berditchevski, Fedor**	**Studying immune microenvironment in inflammatory breast cancer**	**University of Birmingham**	**PENDING**		
NIB16-0227	**30/11/2016**	**Longley, Dan**	**Impact of chemotherapy on anti-cancer immunity in molecularly-stratified subgroups of colorectal cancer**	**CCRCB, QUB**	**PENDING**		

NIB16-0228	**02/12/2016**	**Rima, Bert**	**Validation of a mutation leading to immunodeficiency**	**QUB Emeritus Professor**	**REJECTED**		
NIB16-0229	**13/02/2017**	**Turkington Richard**	**Investigation of Circulating Haematological Biomarkers in Cancer (ICHOR)**	**CCRCB, QUB**	**PENDING**		
NIB17-0230	**06/02/2017**	**Sloan, Philip**	**Clinical outcomes in acinic cell carcinoma and salivary secretory carcinoma**	**Cellular Pathology, Newcastle upon Tyne Hospitals NHS Foundation Trust**	**APPROVED – PENDING COMPLETION OF MTA**		
NIB17-0231	**09/03/2017**	**Gonzales de Castro, David**	**Validation of an NGS approach to detect sarcoma fusions in FFPE and ctDNA**	**CCRCB, QUB**	**PENDING**		
NIB17-0232	**13/01/2017**	**Buckley, Niamh**	**Developing a companion diagnostic test to stratify patients based on a BRCA1/Pin1/Lyn signalling axis to predict response in triple negative breast cancer**	**CCRCB, QUB**	**PENDING**		
NIB17-0233	**13/02/2017**	**McDowell, Andrew**	**Mapping the genotypes of P. acnes strains colonising cancerous prostate tissue**	**NI Centre for Stratified Medicine, Clinical Translational Research & Innovation Centre, Londonderry**	**PENDING**		
NIB17-0234	**06/02/2017**	**Dunne, Philip**	**Identification of prognostic biomarkers in the fibroblast-rich subtype of colorectal cancer**	**CCRCB, QUB**	**PENDING**		
NIB17-0235	**13/02/2017**	**Beirne, James**	**The discovery and evaluation of disease-specific biomarkers for Epithelial Ovarian Cancer**	**CCRCB, QUB**	**PENDING**		

6. Declaration

Signature of tissue bank manager:	
Date of submission:	31 March 2017