School of Medicine success with new HRB Applying Research into Policy and Practice (ARPP) Postdoctoral Fellowships 2018 programme

The School of Medicine is delighted to congratulate 5 researchers from the school who have secured awards under the HRB Applying Research into Policy & Practice Postdoctoral Fellowships (ARPP) 2018 programme. The HRB ARPP is a new programme, and 2018 marks the inaugural launch of the first call.

The programme whose objective is Building the capability and leadership potential in applied health research attracted a total, from all HEIs, of 29 eligible applications - 13 were in the In-practice arm and 16 were in the Academic arm. Following an international peer-review, a shortlist of 17 applicants were invited to interview on 11 and 12 September 2018. Of the 17 called for interview, 6 were from the School of Medicine, Trinity College. The final HRB Board approval of the interview panel recommended the following 5 proposals for an award.

1. “HPV associated disease: shaping the future prevention and management pathway”

Lead PI: Christine White  
Mentor: John O’Leary

HPV vaccination and HPV primary screening will change the landscape of HPV associated disease. Cervical cancer accounts for the vast majority of HPV associated cancers. It is now increasingly recognised that HPV is also implicated in other anogenital cancers including vulvar, vaginal, anal and penile. HPV vaccination will reduce the burden of HPV-associated diseases. However, HPV vaccination is not a panacea, and consideration of the implications of HPV vaccination is required. HPV primary cervical screening will be implemented in 2019. However, choosing an appropriate triage strategy for HPV positive women remains a key challenge. HPV-PATH will build on existing work from the CERVIVA HPV Primary Screening Study, which describes a panel of molecular markers for triaging HPV positive women. This study will embed within CervicalCheck, and apply the data on triage tests to the entire screening population [vaccinated/unvaccinated], generating data for defining optimal triage approaches for HPV positive women.

HPV vaccination will reduce the burden of other anogenital cancers. However, there is currently no data relating to HPV prevalence in anogenital cancers in Ireland. This creates difficulties in identifying the impact of HPV vaccination on non-cervical cancers. A population-based study on the epidemiology of HPV infection in other anogenital cancers, will be carried out, starting with vulvar cancer. This will build evidence around HPV vaccination and the potential impact on vulvar cancer.

Furthermore, anogenital cancers require further molecular characterisation. In parallel with HPV, p53 mutation appears to assume an important role in anogenital cancers. p53 and HPV molecular characterisation is required to further define distinct disease groups in anogenital cancers. HPV-PATH will characterise vulvar cancers based on HPV and p53 status and identify if distinct clinicopathological groups exist.

Ultimately, this research will generate actionable knowledge that can be translated to practice and policy for improved delivery in healthcare of HPV-associated diseases.
2. “Exploring the immunome of oesophageal adenocarcinoma using bioinformatics to assess and predict responses to neoadjuvant therapy (Immune-AEGIS)”

Lead PI: Claire Donohoe  
Mentor: John Reynolds

Despite treatment advances, the five-year survival of patients diagnosed with oesophageal adenocarcinoma (OAC) remains <20%.

In many solid tumours with good prognoses such as breast and colon, the immune contexture including the density, composition, organisation and functional state of the immune infiltrate of tumours is prognostic and predictive of treatment response. The genomic landscape of OAC is complex with a high mutation burden2 and a large number of point mutations that occur at very low frequency. Immunogenicity of tumours relies on the combination of antigenicity (due to neoepitopes on the cancer cells) and adjuvanticity (from specific Damage Associated Molecular Patterns – endogenous molecules emitted by stressed or dying cells) which together stimulate an immune response.

A response to immunotherapy is partly predicted by a higher mutation load but a lower load does not preclude a response. The higher mutational load is thought to reflect a higher prevalence of neoepitopes which result in a greater T cell response making OAC an attractive model to assess immune responses.

Using bioinformatics techniques, this study will use publically available whole genome sequences to identify prognostically-relevant immune cells in OAC. This signature will be validated using histologic samples from a large biorepository in addition to drawing from samples collected as part of the international NeoAEGIS RCT comparing neoadjuvant chemoradiotherapy to chemotherapy. Having defined the most clinically relevant immune infiltrate this will be used to assess whether it impacts on the longterm prognosis of patients with complete regression following neoadjuvant therapy - to identify upfront those in need of further treatment to prevent recurrence. It will also be used to assess whether radiation treatment or chemotherapies induce immunogenic cell death, thus opening avenues for the combination of immune with standard therapies.

Budget: €243,711.00 over 36 months


Lead PI: Lorna Roe  
Mentor: Dominic Trepel

Background: Healthcare needs and service use increase with frailty. Frailty is closely linked with cognitive impairment, but not all those who are cognitively impaired are frail. It is not well understood how the combination of frailty and cognitive impairment are related to patterns of illness, service use and cost of care.

Aim: We will use data from the Irish Longitudinal Study on Ageing (TILDA) to examine:
1. The prevalence of physical and cognitive frailty and incident risk of severe cognitive impairment
2. The drivers of patterns and costs of care
3. Variation in caregiver type and intensity of informal care provided

**Methods:** We aim to use data from wave 1 to wave 5 of the Irish Longitudinal Study on Ageing (TILDA). Respondent's socio-economic data, health data (frailty, chronic illness, disability, falls, and measures of cognition) and healthcare utilisation (primary, secondary, long term care, medication, and informal care) will be used.

In the context of future pressures on public budgets from population ageing, examining the determinants of healthcare utilisation and costs with frailty and cognitive impairment can assist policymakers in designing appropriate interventions (e.g., increasing use of primary prevention) to control expenditure, improve population health and better project the effects of demographic and socioeconomic change on healthcare needs and use.

**Budget:** €229,466.20 over 36 months

4. “Economics of palliative care: from international evidence to Irish policy”

**Lead PI:** Peter May
**Mentor:** Charles Normand

**Rationale:** People with complex medical illness are the most significant challenge facing 21st century healthcare. Palliative care (PC) aims to improve outcomes for seriously-ill people through interdisciplinary, patient-centred decision-making. Current policy suggests that Ireland could be the first country to legislate for universal PC provision on the basis of need. Economic evidence on policy options is limited.

**Aims and objectives:** The primary aim of this study is to estimate the costs of national universal PC provision and compare these with current provision. This aim will be achieved through:
1. Analysis of cohort study data from Ireland and internationally to improve understanding of when and for whom PC impacts patterns of care
2. Econometric modelling to estimate and compare costs (societal perspective) of current and proposed policy options, 2021-2046

**Methods and data:** Cohort study analysis incorporates multiple available datasets. Associations between PC and costs will be evaluated using nonlinear models, segmenting samples by baseline characteristics. Then a demographic and economic simulation model will be developed, estimating the societal costs of universal provision and comparing this to current provision. Estimates will take into account health states and utilisation among older people in Ireland with PC needs, changing needs due to demographic ageing, the cost of universal provision, and estimates of how universal provision would impact costs overall. Data will be drawn from a subsample of older adults with PC need in The Irish Longitudinal study on Ageing (TILDA).

**Output:** The primary output will be a report estimating the cost-effects to Ireland of implementing universal PC provision on the basis of need (compared to not doing so and retaining current provision). This proposal has been devised in consultation with the Department of Health and would feed directly into current policymaking.

**Budget:** €222,998.00 over 36 months
5. “Informing Chronic Kidney Disease health policy in Ireland: Linkage of large datasets to study the interaction between ageing and kidney function”

Lead PI: Donal Sexton
Mentor: Dr Conall O'Seaghdha

The Irish longitudinal Study on Ageing began in 2009 with wave 1 and has now completed 4 waves. There are over 1 million data points for over 8,500 participants. This is a random sample of the Irish population and therefore is very representative of community dwelling individuals in Ireland. As a result, findings of TILDA are directly translatable to the Irish population and has considerable potential for informing and transforming public health and health care policy in Ireland.

Data collection in TILDA has now reached a stage where data mining and big data techniques may unearth valuable insights, particularly for the integration of different forms of data such as demographic and economic data with biomarker, biometric and genetic data. The first objective of this project is to explore the relationship between kidney function and cardiac function using data obtained by the Finometer. We will then go on to use machine learning techniques to model and incorporate TILDA data in order to gain insights into such outcomes as kidney disease, syncope, injurious falls, death, hospitalisation, nursing home and care facility admission and medication usage over time. Synergistic with these aims Dr Sexton is also involved in clinical research involving the use of smart phone/device applications to both study and improve outcomes for patients with end stage kidney disease treated by both Haemodialysis and Peritoneal dialysis. The second part of this grant, which will be undertaken in collaboration with Brigham and Women’s Hospital and Harvard Medical School Boston USA, is to explore the use of big data being collected by these smart phone applications. The objective from the resulting data analysis is to gain insights into the care of patients with chronic diseases such as kidney failure treated with a kidney transplant or dialysis. The training objective of this grant will be to help Dr Sexton become an independent investigator and an expert in big data applications.

Budget: €134,438.00 over 36 months

The School of Medicine is delighted to congratulate 5 researchers from the school who have secured awards under the HRB Applying Research into Policy & Practice Postdoctoral Fellowships (ARPP) 2018 programme. The HRB ARPP is a new programme, and 2018 marks the inaugural launch of the first call.

The programme whose objective is Building the capability and leadership potential in applied health research attracted a total, from all HEIs, of 29 eligible applications - 13 were in the In-practice arm and 16 were in the Academic arm. Following an international peer-review, a shortlist of 17 applicants were invited to interview on 11 and 12 September 2018. Of the 17 called for interview, 6 were from the School of Medicine, Trinity College. The final HRB Board approval of the interview panel recommended the following 5 proposals for an award.

1. “HPV associated disease: shaping the future prevention and management pathway”

Lead PI: Christine White
Mentor: John O’Leary
HPV vaccination and HPV primary screening will change the landscape of HPV associated disease. Cervical cancer accounts for the vast majority of HPV associated cancers. It is now
increasingly recognised that HPV is also implicated in other anogenital cancers including vulvar, vaginal, anal and penile. HPV vaccination will reduce the burden of HPV-associated diseases. However, HPV vaccination is not a panacea, and consideration of the implications of HPV vaccination is required.

HPV primary cervical screening will be implemented in 2019. However, choosing an appropriate triage strategy for HPV positive women remains a key challenge.

HPV-PATH will build on existing work from the CERVIVA HPV Primary Screening Study, which describes a panel of molecular markers for triaging HPV positive women. This study will embed within CervicalCheck, and apply the data on triage tests to the entire screening population [vaccinated/unvaccinated], generating data for defining optimal triage approaches for HPV positive women.

HPV vaccination will reduce the burden of other anogenital cancers. However, there is currently no data relating to HPV prevalence in anogenital cancers in Ireland. This creates difficulties in identifying the impact of HPV vaccination on non-cervical cancers. A population-based study on the epidemiology of HPV infection in other anogenital cancers, will be carried out, starting with vulvar cancer. This will build evidence around HPV vaccination and the potential impact on vulvar cancer.

Furthermore, anogenital cancers require further molecular characterisation. In parallel with HPV, p53 mutation appears to assume an important role in anogenital cancers. p53 and HPV molecular characterisation is required to further define distinct disease groups in anogenital cancers. HPV-PATH will characterise vulvar cancers based on HPV and p53 status and identify if distinct clinicopathological groups exist.

Ultimately, this research will generate actionable knowledge that can be translated to practice and policy for improved delivery in healthcare of HPV-associated diseases.

**Budget:** €243,711.00 over 36 months

**2. “Exploring the immunome of oesophageal adenocarcinoma using bioinformatics to assess and predict responses to neoadjuvant therapy (Immune-AEGIS)”**

**Lead PI:** Claire Donohoe  
**Mentor:** John Reynolds

Despite treatment advances, the five-year survival of patients diagnosed with oesophageal adenocarcinoma (OAC) remains <20%.

In many solid tumours with good prognoses such as breast and colon, the immune contexture including the density, composition, organisation and functional state of the immune infiltrate of tumours is prognostic and predictive of treatment response. The genomic landscape of OAC is complex with a high mutation burden and a large number of point mutations that occur at very low frequency.

Immunogenicity of tumours relies on the combination of antigenicity (due to neoepitopes on the cancer cells) and adjuvanticity (from specific Damage Associated Molecular Patterns – endogenous molecules emitted by stressed or dying cells) which together stimulate an immune response.

A response to immunotherapy is partly predicted by a higher mutation load but a lower load does not preclude a response. The higher mutational load is thought to reflect a higher prevalence of neoepitopes which result in a greater T cell response making OAC an attractive model to assess immune responses.

Using bioinformatics techniques, this study will use publicly available whole genome sequences to identify prognostically-relevant immune cells in OAC. This signature will be validated using histologic samples from a large biorepository in addition to drawing from samples collected as part of the international NeoAEGIS RCT comparing neoadjuvant
Chemoradiotherapy to chemotherapy. Having defined the most clinically relevant immune infiltrate this will be used to assess whether it impacts on the longterm prognosis of patients with complete regression following neoadjuvant therapy - to identify upfront those in need of further treatment to prevent recurrence. It will also be used to assess whether radiation treatment or chemotherapies induce immunogenic cell death, thus opening avenues for the combination of immune with standard therapies.

**Budget:** €261,702.00 over 60 months

3. **“The Frail Brain and the Frail Body: Impact of FRAILty and COGnitive impairment on trajectories, patterns and costs in care in old age”**

**Lead PI:** Lorna Roe  
**Mentor:** Dominic Trepel

**Background:** Healthcare needs and service use increase with frailty. Frailty is closely linked with cognitive impairment, but not all those who are cognitively impaired are frail. It is not well understood how the combination of frailty and cognitive impairment are related to patterns of illness, service use and cost of care.

**Aim:** We will use data from the Irish Longitudinal Study on Ageing (TILDA) to examine:  
1. The prevalence of physical and cognitive frailty and incident risk of severe cognitive impairment  
2. The drivers of patterns and costs of care  
3. Variation in caregiver type and intensity of informal care provided

**Methods:** We aim to use data from wave 1 to wave 5 of the Irish Longitudinal Study on Ageing (TILDA). Respondent’s socio-economic data, health data (frailty, chronic illness, disability, falls, and measures of cognition) and healthcare utilisation (primary, secondary, long term care, medication, and informal care) will be used.

In the context of future pressures on public budgets from population ageing, examining the determinants of healthcare utilisation and costs with frailty and cognitive impairment can assist policymakers in designing appropriate interventions (e.g., increasing use of primary prevention) to control expenditure, improve population health and better project the effects of demographic and socioeconomic change on healthcare needs and use.

**Budget:** €229,466.20 over 36 months

4. **“Economics of palliative care: from international evidence to Irish policy”**

**Lead PI:** Peter May  
**Mentor:** Charles Normand

**Rationale:** People with complex medical illness are the most significant challenge facing 21st century healthcare. Palliative care (PC) aims to improve outcomes for seriously-ill people through interdisciplinary, patient-centred decision-making. Current policy suggests that Ireland could be the first country to legislate for universal PC provision on the basis of need. Economic evidence on policy options is limited.

**Aims and objectives:** The primary aim of this study is to estimate the costs of national universal PC provision and compare these with current provision. This aim will be achieved through:
1. Analysis of cohort study data from Ireland and internationally to improve understanding of when and for whom PC impacts patterns of care  
2. Econometric modelling to estimate and compare costs (societal perspective) of current and proposed policy options, 2021-2046
Methods and data: Cohort study analysis incorporates multiple available datasets. Associations between PC and costs will be evaluated using nonlinear models, segmenting samples by baseline characteristics. Then a demographic and economic simulation model will be developed, estimating the societal costs of universal provision and comparing this to current provision. Estimates will take into account health states and utilisation among older people in Ireland with PC needs, changing needs due to demographic ageing, the cost of universal provision, and estimates of how universal provision would impact costs overall. Data will be drawn from a subsample of older adults with PC need in The Irish Longitudinal study on Ageing (TILDA).

Output: The primary output will be a report estimating the cost-effects to Ireland of implementing universal PC provision on the basis of need (compared to not doing so and retaining current provision). This proposal has been devised in consultation with the Department of Health and would feed directly into current policymaking.

Budget: €222,998.00 over 36 months

5. “Informing Chronic Kidney Disease health policy in Ireland: Linkage of large datasets to study the interaction between ageing and kidney function”

Lead PI: Donal Sexton
Mentor: Dr Conall O’Séaghdha

The Irish longitudinal Study on Ageing began in 2009 with wave 1 and has now completed 4 waves. There are over 1 million data points for over 8,500 participants. This is a random sample of the Irish population and therefore is very representative of community dwelling individuals in Ireland. As a result, findings of TILDA are directly translatable to the Irish population and has considerable potential for informing and transforming public health and health care policy in Ireland.

Data collection in TILDA has now reached a stage where data mining and big data techniques may unearth valuable insights, particularly for the integration of different forms of data such as demographic and economic data with biomarker, biometric and genetic data. The first objective of this project is to explore the relationship between kidney function and cardiac function using data obtained by the Finometer. We will then go on to use machine learning techniques to model and incorporate TILDA data in order to gain insights into such outcomes as kidney disease, syncope, injurious falls, death, hospitalisation, nursing home and care facility admission and medication usage over time. Synergistic with these aims Dr Sexton is also involved in clinical research involving the use of smart phone/device applications to both study and improve outcomes for patients with end stage kidney disease treated by both Haemodialysis and Peritoneal dialysis. The second part of this grant, which will be undertaken in collaboration with Brigham and Women's Hospital and Harvard Medical School Boston USA, is to explore the use of big data being collected by these smart phone applications. The objective from the resulting data analysis is to gain insights into the care of patients with chronic diseases such as kidney failure treated with a kidney transplant or dialysis. The training objective of this grant will be to help Dr Sexton become an independent investigator and an expert in big data applications.

Budget: €134,438.00 over 36 months