



“Exploiting Discovery To Theranostics”



PROGRESS REPORT DEC 2011

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
RESEARCH OUTPUTS	4
EDUCATIONAL VALUE OF EMER CASEY FUNDING	9
FUTURE PROJECTS	12
CONTACT DETAILS	13

EXECUTIVE SUMMARY

The support of the Emer Casey Foundation has enabled the DISCOVERY consortium to make significant progress in the fight against ovarian cancer and the consortium are deeply grateful for this funding. 2011 has been a successful year for the consortium with a major highlight being the publication [Egan et al, 2011] in PLoS ONE, one of the top scientific journals. This publication outlined the importance of platelets in cancer metastasis using ovarian cancer as a model. The idea of platelets cloaking tumour cells and preventing them from being recognised by the immune system has now gained significant interest in the scientific community and is becoming the subject of high impact publications. The support of the foundation led to the enabling work for this study and assisted the consortium in attracting funding from Science Foundation Ireland to continue this work as part of the Biomedical Devices Institute-2 [BDI-2] SFI CSET [Centres for Science Engineering and Technology]. This programme [Oncology 1] is examining circulating tumour cells [CTCs] in ovarian and other cancer models.

The Emer Casey fellows have had a busy year as all three have now generated substantial results which they have presented at national and international meetings. Lynda McEvoy and Mairead Murphy are due to complete their PhDs in the first quarter of 2012 and have very exciting and novel results to present.

Mairead Murphy presented some of her initial results at the Ovarian Cancer Screening Meeting in London in November 2011. Her work examining auto antibody profiles in ovarian cancer generated significant interest from the diagnostic industry as this technology is now a major focus of interest in ovarian cancer diagnostics. This is a major boost to the consortium and to Mairead and we are currently in discussion with Roche diagnostics and Ayanda Biosystems to take this forward.

The work supported by the Emer Casey foundation has now produced a hugely important set of biomarkers that can be taken to develop a diagnostic and therapeutic platform in collaboration with industry partners.

Lynda McEvoy has generated some very exciting results in relation to the development of chemoresistance and is currently examining patient samples from the bioresource for these novel markers. Lynda has presented her work at national and international meetings this year.

Brendan Ffrench has successfully isolated cancer stem cells in an ovarian cancer model and is currently validating this in his mouse studies. This groundbreaking work will have important implications in the treatment of cancer and we look forward with anticipation to these results.

In addition to concentrating on their own project, the fellows have also been developing their future research careers and gaining important supervisory skills. They have been involved in supervising medical and science students detailed below. The research carried out by the consortium has made an enormous contribution to the scientific community and has resulted in 19 peer reviewed articles and 32 abstracts listed below. This work has been presented at both national and international conferences and generated enormous interest from the scientific and pharmaceutical community.

RESEARCH OUTPUTS [PEER REVIEWED PUBLICATIONS]

Murphy MA*, O'Connell DJ*, O'Kane SL, O'Brien JK, O' Toole S, Martin C, Sheils O, O'Leary JJ, Cahill DJ. Epitope presentation is an important determinant of the utility of antigens identified from protein arrays in the development of autoantibody diagnostic assays. [submitted Nov 2011] [*Joint first authors].

Murphy MA, O'Leary JJ, Cahill D. Cloak and Dagger: Profiling the interplay of cancer with the immune system. [submitted Nov 2011]

D'Adhemar CJ, Gallagher MF, O'Toole S, Murphy C, Smyth PC, Stordal B, Crowley D, Cooke AA, Martin C, Sheils O, O'Leary JJ. The MyD88+ phenotype is an adverse prognostic factor in epithelial ovarian cancer [submitted].

Laios A*, Mohamed BM*, Kelly L, Flavin R, McEvoy L, Martin C, Sheils O, Gallagher M, Ring M, Davies T, Mc Guinness EPJ, Gleeson NC, D'Arcy T, Sheppard BL, O'Leary JJ, O'Toole SA. Pre-treatment of ovarian cancer cell lines with an MMP-9 inhibitor prior to cisplatin treatment increases cytotoxicity as determined by high content screening cell-based assays [submitted] [*Joint first authors].

Sheils O, Crowley D, O'Toole S, Smyth P, Martin C, Norris L, Laois A, Flavin R, Conlon N, McEvoy L, Finn S, O'Leary JJ. Examining the relationship between expression of tumour expressed genes, patient platelet count, disease free period and survival [submitted].

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ABSTRACTS

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EDUCATIONAL VALUE OF EMER CASEY FUNDING:

The funding from the Emer Casey foundation has allowed DISCOVERY to add educational value and in addition to the three PhD fellows the following projects have been undertaken which support the work of the fellows:

- **4TH year medical student [UCC]**

Ann Marie Coughlan joined the group for a short research project as part of her medicine degree. Her project focused on elucidating the mechanism of action of MMP9 in chemoresistant ovarian cancers. Initial work by the consortium established MMP9 as an important marker in chemoresistance of ovarian cancer and Ann Marie examined this closer by also investigating an inhibitor of MMP9 and a regulator of MMP9. She found all markers increased in recurrent tumours and this work feeds into ongoing work into this molecule by the group. Ann Marie gained valuable laboratory experience, writing and presentation skills during her time with the group.

- **Dublin City University (Biomedical Diagnostics Institute) MSc Students**

The Emer Casey fellows have been involved in the direct laboratory supervision of 3 summer students from BDI-2 in Dublin City University. These projects have yielded valuable pilot results which are now forming the basis of further grant applications and the students gained valuable laboratory experience from the fellows and in turn the fellows gained valuable supervisory experience which will benefit their future research careers.

Student 1 [Padraig Kearney]: The Role of Platelets in Placentation

Padraig's project looked at the role of platelets in placentation. In the process of placentation, trophoblasts invade into the maternal tissue and spiral arteries. This results in the remodelling of the arteries for the purpose of preparing them to efficiently supply blood to the developing fetus. Our work which was recently published in PLoS ONE demonstrated the importance of platelets in the spread of cancer and we thought a similar process may be taking place in early pregnancy. In ovarian cancer we found that the tumour cells could activate platelets and we wanted to determine if trophoblasts [the cells that invade during implantation] could do the same. Padraig did find some evidence for activation of platelets and the ability of platelets to induce changes in the trophoblast. This pilot study will be the basis for a future grant application to investigate this further. Padraig received supervision from the Lynda McEvoy and Brendan Ffrench to enable the successful completion of this project.

Student 2 [Tanya Englishby]: Evaluating the antineoplastic activity of free and formulated sulindac

Tanya also received supervision from the Emer Casey fellows to perform this project. Sulindac is a non steroidal anti inflammatory drug and our group has demonstrated its anti cancer potential in the treatment of cervical cancer and pre cancer. Tanya project was to evaluate various formulations of sulindac and she

found a particular formulation was most effective. Tanya will now apply for an Irish Cancer Society Scholarship to continue this work.

Student 3 [Patrick Kerr]: CERVIVA-HPV testing in the management of women post treatment for high grade cervical dysplasia.

The standard treatment for high grade cervical lesions in colposcopy is LLETZ. However, the risk of disease recurrence post treatment with LLETZ for high grade CIN ranges from 5-35%. Women with evidence of persistent Human Papilloma Virus (HPV) infection following treatment have a higher incidence of disease recurrence than those who clear HPV post-treatment. The aim of this study was to evaluate the utility of HPV DNA and mRNA testing in the follow-up of women post treatment. This work forms part of CERVIVA the Irish cervical screening research consortium and again involved supervisory roles by the fellows.

- **Trinity College Dublin Medical Students**

Funding from the Emer Casey foundation has enabled the extension and maintenance of the DISCOVERY bioresource which has been a valuable resource for many projects ongoing in the laboratory and in particular it has enabled students gain valuable laboratory experience as part of their college education. The bioresource was utilised for 3 second year medicine students (TCD).

Louise Rice and Wan Nornadhirah Wan Rosdi: Examination of MMP-9 nad TIMP-2 in serum from ovarian cancer patients

Louise and Wan Nornadhirah examined the expression of a chemoresistant marker MMP-9 and its inhibitor TIMP-2 in the serum of patients and found that they increased in recurrent disease. This would be a valuable marker to determine this chemoresistance by a blood test and this forms part of a recently submitted paper by the group, Laios et al [Submitted].

Sean Tamqumus: Examination of the role of tissue factor in ovarian cancer

Sean examined the role of tissue factor in ovarian cancer. Tissue factor is responsible for starting the clotting cascade and ovarian cancer is known to be associated with a higher risk of clotting. Sean investigated whether this was due to a higher level of tissue factor being produced by the tumours. He found that clear cell cancers on the ovary produced more tissue factor than other tumor types and clear cell cancers are most at risk of clotting. This work is being continued in the lab as part of an MD project.

- **International Students**

Erasmus Student from Germany [Claudia Gasch]:The role of MyD88 in chemoresistance

Claudia has worked on two projects that are linked to ovarian cancer. In the first, Claudia has knocked down and over-expressed MyD88 in our cancer stem cell model and challenged these cells with ovarian cancer chemotherapy drug cisplatin. The results are to be completed next week. This experiment will define whether MyD88 is required for these cells to resist chemotherapy or not.

In the second experiment Claudia has mixed undifferentiated and differentiated cancer cells. This is to model the biology of a solid tumour, where these cell types are found in the same location. We asked whether the two types of cells co-exist independently or inter-dependently in the tumour. Our results suggest that differentiated cells hinder the proliferation of undifferentiated cells, something that has never before been contemplated, never mind shown. The obvious explanation is that the two cells types A) interact with each other B) secrete molecules that influence each others' growth or C) both. To test B we grew differentiated cells in media for 24 hours to generate 'conditioned media'. We added this conditioned media to undifferentiated cells to see whether the secreted products of the differentiated cells are sufficient to influence proliferation. After one week they were not. Two week data is pending. The results suggest that the presence of differentiated cells is required for this suppression of proliferation

- **PRTL I PhD Rotation Project Student**

Fintan Geoghan: Knockdown of MyD88 in an ovarian cancer model

Fintan is blocking the expression of MyD88 in an ovarian cancer model and determining whether he can make the cells more sensitive to chemotherapy. This has important implications for patients who become resistant to chemotherapy.

- **Doctorate Students**

The work carried out by the Emer Casey fellows has allowed DISCOVERY to also enhance education for doctorate students and currently 4 clinical lecturers are carrying out PhDs and MDs working closely with the fellows; Charles D'Adhemar, Aoife Canney, Niamh Conlon and Feras Saadeh.

FUTURE PROJECTS:

The DISCOVERY consortium looks forward to the opportunity of presenting future novel and exciting project ideas to the Emer Casey foundation.

It is our objective to address the compelling issues of ovarian cancer with a view to:

- (a) Discovering novel markers for diagnosis, prognosis and response prediction
- (b) Better understanding the disease
- (c) Developing prognostic indicators to assist patient management
- (d) Identifying patients who will benefit from existing chemotherapeutic intervention
- (e) Discovering novel therapeutic targets

DISCOVERY will comply with Government's Strategy for Science, Technology and Innovation (SSTI) 2006-2013. Implicit in the strategy is the recognition that a strong research culture is vital if the health service is to offer a world-class standard of care to patients and retain professionals of the highest quality. This strategy is intrinsic to our studies. The consortium provides an unparalleled opportunity to facilitate and catalyse world class research.

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