Kathleen Cuningham Foundation **kConFab** CONsortium for research into FAmilial Breast Cancer

22nd March 2017

Dear Emer Casey Foundation members

We would like to give you a progress report on the new research projects we outlined to you last year.
Work has moved quickly over the past 12 months due to the momentum that has built over a few years and there are many important updates for you.

<u>Progress to date.</u>

1. The search for new ovarian cancer genes. This has been a major initiative ours for at least 10 years. The use of new technology and combining our DNA samples from ovarian cancer patients with 32 other similar groups from the USA, UK and Europe to obtain statistical power, has resulted in two new genes associated with ovarian cancer being found. One gene is known as *RAD51D*, the other as *BRIP1*. We have demonstrated that they are not as frequently found as a *BRCA1* or *BRCA2* gene mutation but they still account for a 5-12% and 10-15% life time risk, respectively. Clinic testing for these two genes isn't available at the moment as we are working as a joint body internationally on the clinical management guidelines as to how to manage these gene carriers, i.e., breast screening advice and cancer prevention strategies such as surgical intervention. It is hoped that within 2 years mutation notification will occur to known carriers, females and males, nationally via kConFab.
   We have talked previously about the new gene targeted PARPi therapies for ovarian cancer patients who carry a *BRCA1* and *BRCA2* gene mutation, and how effective and well tolerated this treatment can be. The good news is that the *RAD51D* and *BRIP1* gene faults may also be sensitive to the PARPi inhibitors as these genes lie in the same "gene signalling pathway" as the *BRCA1* and *BRCA2* genes. This treatment is having expanded use across ovarian, breast and prostate cancer patients who are *BRCA1* and *BRCA2* mutation carriers and it is encouraging to think that other gene mutation carriers may be suitable for this improved cancer treatment in the very near future.

2. We have chatted over the past 2 years about our discovery of *super survivors* of ovarian cancer - 10+ years due to being sensitive to platinum based chemotherapy, vs. poor responders who unfortunately fail all treatments. Our understanding in this area is moving fast:

a) We are constantly keeping in touch with all of our ovarian cancer patients to see how they are responding to their treatments and collecting new biological samples and treatment details to be used in our active research studies. Increasing our numbers of both patient types, super responders vs. poor responders, is helping us gain new information in this area of research.
b) Our work with Fox Chase in the USA has expanded. We mentioned last year that we had discovered an inhibitor (known as spliceosome inhibitors) that can modify the gene fault and prevent drug resistance in patients who carry a *BRCA1* gene fault in a particular location within the gene, known as exon 11. This work has now discovered 3 different classes of inhibitors can be effective in treating ovarian cancer, hence, high-lighting which patient may not respond to treatment (if their genetic fault/mutation lies in exon 11)and guide better and more well tolerated drug treatments.
c) We are exploring whether the position and type of *BRCA1 or BRCA2* gene fault (mutation) is affecting a patient's outcome to treatment as there are 100s of gene faults (mutations) that occur in both the *BRCA1* and *BRCA2* gene. We hypothesized that a mutations position in the gene may result in poor patient treatment outcomes. After preliminary analysis, while we didn't see any obvious association, there was a definite trend that mutations located at one end of the *BRCA1* gene were associated with worse survival outcomes than those located at the other end of the *BRCA1* gene. To obtain a definitive answer to the trend we have seen and to gain increased mathematical power for our analysis, we have recruited new ovarian cancer patients over the past 12 months and we will add these new patients mutation data linked to their treatment and clinical outcome for improved analysis.
d) TRACEBACK, presented by Dr Rachel Delahunty at our recent meeting, is a new project that is highly translational, with the practical goal of identifying at-risk relatives of women from the general population, not high risk cancer families, with a diagnosis of ovarian cancer diagnosed over the past 10 years who have missed out on the recent increased understanding of ovarian cancer genetics and revised national testing guidelines. TRACEBACK will identify the barriers to referral and uptake of testing, allowing improvements in prospective testing. Approximately 15-20% of the women identified in TRACEBACK will already be consented to kConFab. Therefore, kConFab will work closely with the TRACEBACK team to identify women in both studies, and, kConFab will share our results so duplication (and leg work) of genetic testing and following up for treatment doesn't occur.
e) CASCADE, our rapid autopsy program, allows us to collect metastatic tissue from ovarian cancer patients who have unfortunately passed away. We started this program 4 years ago as the collection of metastatic tissue is impossible to obtain these days as CT imaging, rather than tissue collection, is the diagnostic preference to determine if a patient has advance disease. As well as having the original primary ovarian cancer tissue, the CASCADE program is further allowing

us to investigate mechanisms of tumour progression and treatment resistance linked to their genetic profile. This program is unique to our group world-wide and is a major driver of advances being made about ovarian cancer. To date, 17 women in total with a diagnosis of ovarian cancer have been involved in the CASCADE program, with 5 new participants included over the past 12 months. This innovative work has just been published in an international high ranking journal *Nature*. An important side benefit of this program has been the positive meaning this program gives to the patients before passing away. It is consistently acknowledged that their lives will end shortly but they know their generous donation will help other women obtain better outcomes for years to come.

Future work.

As our projects are relatively new and gained important momentum over the past 12 months, we are very keen to keep the momentum going with our collaborative national and international group to generate more research results in the projects listed above. In addition, as kConFab has assembled a large unique biological and data resource, which is still building, we have in a positive position to be included in recent discussions with researchers and clinicians about new grant possibilities to explore new research and clinical options for women with ovarian cancer.

On behalf of the national kConFab team, thank you very much for your on-going support of our research program and we wish you all the best with your activities in the coming year.

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