Breast and Ovarian Cancer Research in Australia

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Thematic research area in Australia

The Association for Research between Italy and Australia (ARIA-Queensland) has identified several thematic research areas of mutual interest to both countries. One of the most progressive areas includes research in Breast and Ovarian Cancer. Breast cancer is the 2nd most common cause of cancer death in women and recently has been declared as a world wide epidemic by the World Health Organization (WHO). 1 in 8 women develop breast cancer during their lifetime (statistics: 2003) and this has increased to 1 in 8 women in 2004

Approximately 1 million people worldwide were diagnosed with breast cancer in 2003 with approximately 400,000 deaths per year. Within Australia approximately 11,000 new cases are diagnosed each year with 4,000 deaths. The rate of breast cancer morbidity in Italy for 2004 was a staggering 130,000 deaths representing 27.4 % of all cancer deaths in Italian women!

Breast cancer requires urgent attention in the fields of awareness, diagnosis and treatment.

Resources, funding organizations and their role in Italian collaborations:

In Australia, most of the research in this field is funded by the National Health and Medical Research Council (NH&MRC), the Australian Research Council (ARC) the National Breast Cancer Foundation (NBCF) or independent state funds such as the Queensland Cancer Fund (QCF) and these organizations are keen to promote international research. NBCF, which specializes in the area has recently initiated a national plan for prioritizing Breast cancer research in Australia and is interested to expand this plan include international research, especially in Italy. Their prior interest in the Italian community spans back to 1997 when they funded the project entitled "Development and pilot study of an instrument to determine Italian women's breast cancer early detection practices and beliefs" and they are keen to explore new territory in the fight against breast cancer. Clearly organizations in Italy, such as Telethon are also prioritizing breast cancer research as well. This is apparent by the development and publication of new patient database by key Italian researchers (see below).

Resources, Centres of Excellence in Australia

Institute for Cell and Molecular Therapies at Griffith University: This Institute currently shares facilities with 'Natural Drug Discovery', a partnership with the pharmaceutical company Astra Zeneca. Within this centre is my own research group which has spent several years discovering breast cancer related genes and designing therapeutics to combat the disease.

I am an Australian researcher who has maintained strong research ties with Italian researchers for over 13 years. My research interests over this period have been focused on human disorders. In 1993 I joined Prof. Geraci (CNR, Palermo) to isolate an allergen responsible for the Italian form of Hayfever which effects over 18 million people in Italy and the Mediterranean (Costa et al., 1994). After isolating the gene responsible the combined teams investigated possible drug therapeutics to relieve the symptoms of the disease (Kennedy et al., 1998) and filed a patent for a potential therapeutic ("Anti-allergenic Agent" PCT/AU99/00153 filed 12/03/99). Since my earlier successes in allergen research I focused my research on breast cancer. In 1996 I discovered the G3BP2 gene (Kennedy et al., 1997) and showed its involvement in

cancer pathways (Kennedy et al., 2001) and more specifically in breast cancer (French et al., 2002). My work has been awarded modest international reputation and was recently asked to present a review on the field of his research (Irvine et al., 2004). My discoveries and research into G3BP2 have led to the discovery of several potential anti-breast cancer therapeutics which have been packaged as the "SenoSano" project. A patent which has been filed in Australia, the USA and Europe, including Italy ("Nucleic acids and polypeptides linked to Breast Cancer and uses therefore" PCT/AU02/01136 filed 19/8/02) and is owned jointly by the University of Queensland and the Mater Hospital (see below).
I have also worked in collaboration with Genetic counselors at Griffith University who run one of Australia's only accredited genetic counseling programs, which is convened by Dr Madelyn Peterson, she is keen to discuss counseling strategies with Italians who share similar difficulties in their field.

Peter MacCallum Cancer Institute in Melbourne:
The director of the Peter Mac Cancer Institute, Prof David Bowtell has expressed a strong desire to initiate research interactions with Italian Scientist in the fields of breast and ovarian cancer. The facility he directs represents one of Australia's premier research institutes. The Peter MacCallum institute, in conjunction with QIMR (below) has already been involved in training of Italian scientist Marina Castellano (Castellano et al., 1997; Pavey et al., 2002).

The Gavan Institute in Sydney:
Is one of Australia's key research centres and has a very strong research record in breast cancer. Prof. Rob Sutherland, the Director of the Cancer Research Program is also one of Australia's key breast cancer researchers. (Carroll et al., 2003; Doisneau-Sixou et al., 2003a; Doisneau-Sixou et al., 2003b; Lapillonne et al., 2003; Ormandy et al., 2003; Sutherland and Musgrove, 2004; Swarbrick et al., 2005).

Queensland Institute of Medical Research (QIMR):
This facility is considered Queensland's premier medical research institute. QIMR already houses an active research collaboration between the University of Perugia. Dr Alejandro Lopez of QIMR is currently hosting Marta Sloniecka from the University of Perugia and training her in Dendritic cells techniques which will be used in the field of breast cancer therapeutics. Prof Georgia Chenevix-Trench, also from QIMR, has been instrumental in developing Australia's Kathleen Cuningham Foundation Consortium for Research into Familial Breast cancer and the KConFab database and is keen to share knowledge and training with key Italian researchers who have now developed a similar data base on familial cancers in Italy (Aretini et al., 2003; Marroni et al., 2004a; Marroni et al., 2004b). This is a project that could rapidly generate important data regarding cancer diagnosis and management for both Italy and Australia. Italian medical doctor Stefano Goldwurm (currently at the Parkinson Institute, Milan) was awarded his PhD from QIMR.

Mater Medical Research Institute (MMRI):
The director of MMRI, Prof Derek Hart has already initiated scientific exchanges with two leading Italaian researchers in the field of Dendritic cell research, Dr Paola Ricciardi-Castagnoli (Department of Biotechnology and Bioscience, University of Milano-Bicocca, Milan, Italy) and Antonio Lanzavecchia (currently at the Basel Institute for Immunology). These scientists have been invited to speak at the annual international seminars at the Mater Hospital, Brisbane. Dr Jane Armes has recently

joined MMRI also forms a part of the team investigating anti-breast cancer therapies. Dr Armes team includes ex-Italian Elena Provenzano and have already made significant advances in the field of breast cancer (Provenzano et al., 2003, 2004).

Proposal:

It is readily apparent that there are strong synergies between Italy and Australia in the fields of Breast and Ovarian cancer research that need to be cultivated to maximize their potential. This can be best served by developing a stronger collaboration between key researchers in Italy and Australia. This proposal has only exposed the tip of the iceberg in terms of potential collaborations that can be built on to the mutual benefit of two countries. I am proposing that with sufficient financial support the two countries can enjoy a fruitful exchange of research, technologies and ideas. These exchanges would be served by funding research collaborations between the two countries. These interactions may include, but are not limited to researcher or PhD student exchanges. Collaborations such as these would be enhanced by symposiums in which key researchers from both countries can meet and discuss ideas for future research. The immediate outcomes of this proposal would be the injection of knowledge that the two countries share and the potential to exploit technologies that will ultimately benefit the two countries. A recent report from NHMRC suggested that for every 1 dollar invested in medical research the return was 4 dollars! This is a significant form of investment if the participating countries can spin technologies out of this collaboration!

Bibliography

Aretini, P., D'Andrea, E., Pasini, B., Viel, A., Costantini, R.M., Cortesi, L., Ricevuto, E., Agata, S., Bisegna, R., Boiocchi, M., Caligo, M.A., Chieco-Bianchi, L., Cipollini, G., Crucianelli, R., D'Amico, C., Federico, M., Ghimenti, C., De Giacomi, C., De Nicolo, A., Della Puppa, L., Ferrari, S., Ficorella, C., Iandolo, D., Manoukian, S., Marchetti, P., Marroni, F., Menin, C., Montagna, M., Ottini, L., Pensotti, V., Pierotti, M., Radice, P., Santarosa, M., Silingardi, V., Turchetti, D., Bevilacqua, G., and Presciuttini, S. (2003) Different expressivity of BRCA1 and BRCA2: analysis of 179 Italian pedigrees with identified mutation. Breast Cancer Res Treat 81: 71-79.

Carroll, J.S., Lynch, D.K., Swarbrick, A., Renoir, J.M., Sarcevic, B., Daly, R.J., Musgrove, E.A., and Sutherland, R.L. (2003) p27(Kip1) induces quiescence and growth factor insensitivity in tamoxifen-treated breast cancer cells. Cancer Res 63: 4322-4326.

Castellano, M., Pollock, P.M., Walters, M.K., Sparrow, L.E., Down, L.M., Gabrielli, B.G., Parsons, P.G., and Hayward, N.K. (1997) CDKN2A/p16 is inactivated in most melanoma cell lines. Cancer Res 57: 4868-4875.

Costa, M.A., Colombo, P., Izzo, V., Kennedy, H.D., Venturella, S., Cocchiara, R., Mistrello, G., Falagiani, P., and Geraci, D. (1994) cDNA cloning, expression and primary structure of Par j I, a major allergen of Parietaria Judaica pollen. FEBS. Letters 341: 182-186.

Doisneau-Sixou, S.F., Cestac, P., Faye, J.C., Favre, G., and Sutherland, R.L. (2003a) Additive effects of tamoxifen and the farnesyl transferase inhibitor FTI-277 on inhibition of MCF-7 breast cancer cell-cycle progression. Int J Cancer 106: 789-798.

Doisneau-Sixou, S.F., Sergio, C.M., Carroll, J.S., Hui, R., Musgrove, E.A., and Sutherland, R.L. (2003b) Estrogen and antiestrogen regulation of cell cycle progression in breast cancer cells. Endocr Relat Cancer 10: 179-186.

French, J., Stirling, R., Walsh, M., and Kennedy, H.D. (2002) The expression of Ras-GTPase Activating Protein SH3 domain-binding Proteins, G3BPs, in human breast cancers. Histochemical Journal 34: 223-231.

Irvine, K., Stirling, R., Hume, D., and Kennedy, D. (2004) Rasputin, more promiscuous than ever: a review of G3BP. Int J Dev Biol 48: 1065-1077.
Kennedy, D., Wood, S.A., Ramsdale, T., Tam, P.P., Steiner, K.A., and Mattick, J.S. (1997) Identification of a mouse orthologue of the human ras-GAP-SH3-domain binding protein and structural confirmation that these proteins contain an RNA recognition motif. Biomed Pept Proteins Nucleic Acids 2: 93-99.
Kennedy, D., Colombo, P., Ramsdale, T., Costa, M.A., Duro, G., Izzo, v., Salvadori, S., Guerrini, R., Cochiara, R., Mirisola, M.G., Wood, S.A., and Geraci, D. (1998) Identification of an immunodominant IgE epitope of the Parietaria judaica major allergen. J. Immunology 160: 2780-2785.
Kennedy, D., French, J., Guitard, E., Ru, K., Tocque, B., and Mattick, J. (2001) Characterization of G3BPs: tissue specific expression, chromosomal localisation and rasGAP(120) binding studies. J Cell Biochem 84: 173-187.
Lapillonne, H., Konopleva, M., Tsao, T., Gold, D., McQueen, T., Sutherland, R.L., Madden, T., and Andreeff, M. (2003) Activation of peroxisome proliferator-activated receptor gamma by a novel synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid induces growth arrest and apoptosis in breast cancer cells. Cancer Res 63: 5926-5939.
Marroni, F., Aretini, P., D'Andrea, E., Caligo, M.A., Cortesi, L., Viel, A., Ricevuto, E., Montagna, M., Cipollini, G., Federico, M., Santarosa, M., Marchetti, P., Bailey-Wilson, J.E., Bevilacqua, G., Parmigiani, G., and Presciuttini, S. (2004a) Penetrances of breast and ovarian cancer in a large series of families tested for BRCA1/2 mutations. Eur J Hum Genet 12: 899-906.
Marroni, F., Aretini, P., D'Andrea, E., Caligo, M.A., Cortesi, L., Viel, A., Ricevuto, E., Montagna, M., Cipollini, G., Ferrari, S., Santarosa, M., Bisegna, R., Bailey-Wilson, J.E., Bevilacqua, G., Parmigiani, G., and Presciuttini, S. (2004b) Evaluation of widely used models for predicting BRCA1 and BRCA2 mutations. J Med Genet 41: 278-285.
Ormandy, C.J., Musgrove, E.A., Hui, R., Daly, R.J., and Sutherland, R.L. (2003) Cyclin D1, EMS1 and 11q13 amplification in breast cancer. Breast Cancer Res Treat 78: 323-335.
Pavey, S.J., Cummings, M.C., Whiteman, D.C., Castellano, M., Walsh, M.D., Gabrielli, B.G., Green, A., and Hayward, N.K. (2002) Loss of p16 expression is associated with histological features of melanoma invasion. Melanoma Res 12: 539-547.
Provenzano, E., Hopper, J.L., Giles, G.G., Marr, G., Venter, D.J., and Armes, J.E. (2003) Biological markers that predict clinical recurrence in ductal carcinoma in situ of the breast. Eur J Cancer 39: 622-630.
Provenzano, E., Hopper, J.L., Giles, G.G., Marr, G., Venter, D.J., and Armes, J.E. (2004) Histological markers that predict clinical recurrence in ductal carcinoma in situ of the breast: an Australian population-based study. Pathology 36: 221-229.
Sutherland, R.L., and Musgrove, E.A. (2004) Cyclins and breast cancer. J Mammary Gland Biol Neoplasia 9: 95-104.
Swarbrick, A., Akerfeldt, M.C., Lee, C.S., Sergio, C.M., Caldon, C.E., Hunter, L.J., Sutherland, R.L., and Musgrove, E.A. (2005) Regulation of cyclin expression and cell cycle progression in breast epithelial cells by the helix-loop-helix protein Id1. Oncogene 24: 381-389.

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