Issue 9

National Centre for Asbestos Related Diseases

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Editor | Tracy Hayward

iMig CONFERENCE BIRMINGHAM

The 13th Conference of the International Mesothelioma Interest Group (iMig) held in Birmingham from May 1-4 attracted a record 545 delegates. Eight researchers from NCARD attended, and commented that the Birmingham Convention Centre was "a fantastic venue", that it was "one of the best iMigs ever" and that holding only plenary sessions in the morning meant that there were not too many concurrent sessions, which provided plenty of opportunities to attend talks and to network. Bruce Robinson, Anna Nowak and Richard Lake were all invited chairs. Bruce and Anna also gave plenary sessions, and Scott Fisher gave two presentations.

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There were additionally 9 posters from our Centre, so NCARD research was very well represented and received.

Anna chaired the session on Imaging and gave a talk at the same session as a tag-team with her co-chair, Professor Sam Armato from the University of Chicago. Anna and Sam discussed the limitations of the current criteria for measuring response to treatment in mesothelioma, and the development of a new set of criteria which may solve some of these issues. This session provoked vigorous discussion and many requests for involvement from attending imaging specialists.

Anna also presented the final plenary talk for the conference, wrapping up the immunotherapy session with thoughts on combinations of immunotherapy, combining chemotherapy and radiotherapy with immunotherapy, and how we might improve these treatments for patients.

A more detailed feedback session from attending delegates was held during a bi-weekly NCARD Lab meeting.

Bruce attended Raphael Bueno's session on the exome sequencing of 200 mesotheliomas. More than 90% of the patients had predicted neoantigens, which was encouraging.

ANNA NOWAK AND SAM ARMATO WITH THE BULLRING BULL (OFFICIALLY THE GUARDIAN) BIRMINGHAM.

Sophie had attended a standing room only session on BAP1 mutations from Assunta De Rienzo from Brigham and Womens Hospital. Their research had reflected that BAP1 expression in mesothelioma indicated a lower survival, in contrast to the findings at NCARD and in the literature.

She had been fascinated by the presentation by Michele Carbone from the University of Hawaii, a family study which had traced 100 individuals from a family in Switzerland with familial cancer syndrome and inherited BAP1 mutations. The family had been traced from the 1700s to the United States and an extraordinary 80,000 descendants had been found, living in Texas, two Northern US states and one East Coast state. Descendents indicated multiple cancer malignancies, and raised the question of whether this went some way in explaining the BAP1 mutation in the US, and the power of family studies.

Joost had attended the interim report on the 18 patients enrolled in the Nivolumab trial by Josine Quispel and Paul Baas. Although 8 patients had experienced severe side effects requiring hospitalisation, there were responses from 5 patients and about a 50% disease control rate, sufficiently positive to continue the trial. Richard had chaired a session including Lindsay LaFave from MSKCC Sloan Kettering about BAP1 knockout mice, and Joost attended a session by Lisa Coussens on the relevance of macrophages in mesothelioma. Rafit Hassan's session on phenotyping in T cells showed a higher expression of PDL1 in effusions, while Hannah Moody from Hull University presented research on microRNAs and platinum concentration in lysosomal compartments.

Alistair Cook attended a presentation by Luis De La Maza from Marc de Perrott's lab in Toronto on a project combining radiotherapy and checkpoint blockade. The work is broadly similar to work at NCARD, and quite promising.

Anna reported on a couple of clinical trials of Raffit Hasan's with agents that targeted mesothelin: Amatuximab, Anetumab Ravtansine and CRS-207. All of these agents have shown promise in patients with epithelioid mesothelioma, and the international clinical trials of Amatuximab and Anetumab Ravtansine are opening shortly at Perth's Sir Charles Gairdner Hospital. Peter Slozarek in the UK is proceeding with the AD1-PEG20 ATOMIC mesothelioma trial which will treat almost 400 people, and Luana Calabro in Italy is conducting a trial combining Tremelimumab and Durvalumab, a similar strategy to that used successfully in melanoma.

There have been tantalising stories, some with footage, of Norwegian researcher Oluf Dimitri Røe playing his fiddle, and leading eager scientists and pub crowds alike in rousing renditions of "The Richard Lake Song". But of course, one of the biggest news stories of iMig was Leicester City becoming Premier football champions. Dean Fennell, Liz Darlison, Ian Powley and other local organising committee members and Leicester City fans could not resist listening to the Premier League match, and when the whistle blew, there was a massive cheer. Members of the NCARD delegation, who visited Leicester immediately after iMig for an excellent collaborative discussion, could not have foreseen that the city would be festooned in blue and white, and enjoying a day of historical moment. The final word goes to whoever was overheard declaring "if Leicester City can win the Premier League, we can beat mesothelioma!".

DISTINGUISHED PANELLISTS LAURIE KAZAN-ALLEN AND JIM TE WATER NAUDE, IMIG BIRMINGHAM.

Marie-Claude [Jaurand] and I were having a morning coffee in a cafe in Montparnasse. [I had been visiting Paris to give a talk or something] and we discussed the lack of mesothelioma reagents [cell lines etc], the lack of international cooperation and the absence of a forum to share ideas. Hence IMIG was born. We both agreed that we didn't want an 'organisation', but a loose interactive group without much formality, which is why the term 'interest group' was used."

BRUCE ROBINSON

TRADITIONAL SCIENTIFIC EXCHANGE. FROM LEFT: DR JOAQUIN ZACARIAS-CABEZA (MRC TOXICOLOGY UNIT, LEICESTER); DR HENRY STEER (GLOUCESTERSHIRE HOSPITALS – AND PREVIOUSLY A VISITING RESEARCH FELLOW AT NCARD); DR XIAO-MING SUN (MRC TOXICOLOGY UNIT); PROFESSOR STEVE MUTSAERS (INSTITUTE FOR RESPIRATORY HEALTH, PERTH); DR SCOTT FISHER (NCARD); DR MARION MACFARLANE AND DR TATYANA CHERNOVA (MRC TOXICOLOGY UNIT); AND ALISTAIR COOK (NCARD).

A Profile of Joost Lesterhuis

This article was written by Bruce Heilbuth from BWD Creative in Sydney for the Cure Cancer website, and is reprinted here with permission of both the author and the Cure Cancer organisation.

Malignant pleural mesothelioma is a fatal cancer of the lungs caused by inhalation of asbestos particles. It starts in the lining of the lungs, but once diagnosed often becomes rapidly invasive, growing into the heart and ribcage and causing severe shortness of breath and pain. With his Cure Cancer Australia grant, Dr Willem Joost Lesterhuis (known as Joost) of the National Centre for Asbestos Related Diseases at the University of Western Australia is studying mesothelioma to discover what makes it so invasive.

In this project he will compare how cells in invasive and non-invasive mesotheliomas use their genes to communicate with each other. "To do this I'll use genetic information from model tumours as well as from tissues donated by patients," he explains.

Joost's ultimate goal is to identify new treatments that stop the cancer's invasion. So far he and his team have identified several genes that appear to be promising subjects for therapy. Now they need to test whether these genes are indeed responsible for the invasion and then develop drugs to target them.

Forty-year-old Joost is originally from The Netherlands where he attended medical school and completed his PhD in tumour immunology. He moved to Perth because he was attracted by the excellent research being done at the National Centre for Asbestos Related Diseases at the UWA. (Western Australia, where asbestos was historically mined, has one of the highest mesothelioma rates in the world).

Like many of his contemporaries, Joost believes that, to succeed, researchers must display creativity, stubbornness and perseverance in addition to a capacity for hard work. He also believes it's vital to keep a steady eye on the finish line: "to get treatments into patients, and not stop at intermediate goals like publications and presentations, which is where academic pressure could lead you."

Joost is yet another young researcher who acknowledges the difficulties in getting funding for medical research, particularly for early-to-mid career scientists and for innovative work that by definition is more risky. Funding tends to favour research that's already far-advanced and that has "a large chance of finding an incremental effect," he says.

"I do think it's very important at the same time to fund research that's still preliminary but has a small chance of finding a big effect. Because Cure Cancer Australia awards the researcher rather than the project, it allows them to do that more risky research for which they can't find funding anywhere else."

As a practising oncologist, Joost has noticed a big gap between the almost weekly excitement in scientific papers in big journals reporting on advances made in cancer biology, and the still-dismal prognosis many patients have. "Often the step to the clinic is never made, or the findings are biologically very interesting but don't translate into a clinical application, at least not in the short term."

Now that he's made the transition to full-time researcher he wants to bridge that gap so his laboratory findings can really benefit patients. An inspiring example for him is biochemist Barnett Rosenberg, who in the 1960s stumbled upon the anti-cancer effects of platinum drugs.

JOOST LESTERHUIS IN NCARD LAB. PHOTO: TRACY HAYWARD

"The story goes that when he realised the anti-cancer potential, he nagged his clinical colleagues for years to test it in patients. It's now the most widely used form of chemotherapy and has saved many lives."

"Scientists who go out of the comfort zone of their own research area are inspiring to me. Medical researchers are just as much inventors as they are scientists."

With his colleagues, Joost has shown that, in contrast to common belief, chemotherapy and immune therapy can actually reinforce each other. They have now initiated a clinical trial in mesothelioma patients to see whether this can be an effective new treatment strategy.

Married with three kids, Joost and his wife Dorit love camping, surfing and reading.

SHORT NEWS, BIG STORIES

ICI TRAVEL BURSARIES WON

Congratulations to PhD students Rachael Zemek and Anthony "Buzz" Buzzai for winning Australian Society for Immunology travel bursaries to attend the International Congress for Immunology 2016, to be held in Melbourne in August. Of the 210 bursaries awarded, just 14 went to Western Australian applicants, so well done Rachael and Buzz!

MURDOCH TEACHING RECOGNITION

Wayne Aston, an NCARD PhD student, was ranked within the top 10% of teaching staff based on student surveys for the Murdoch Learning and Teaching award at Murdoch University for 2015. Wayne was a tutor in a first year science foundation unit, Building Blocks for Science Students, designed to assist with the transition from high school to university learning. The ranking is based on surveys submitted by students that cover teaching skills including knowledge of subject area, communication and motivational skills, approachability and the ability to implement effective learning strategies.

ASMR

Seven NCARD students presented at this year's Australian Society for Medical Research (ASMR) WA Scientific Symposium held at Curtin University on 7 June. They were PHD students Sophie Sneddon, Wayne Aston, Rachael Zemek and Laura Wainman; and Honours students Caitlin Tilsed, Emma Port, and visiting student from the Netherlands, Rutger van Röring.

Both Caitlin Tilsed and Laura Wainman received prizes for their presentations at the gala dinner held at the Duxton Hotel: Silver awards with $500 prize money.

ASMR DINNER, DUXTON HOTEL PERTH. SEATED, FROM LEFT: LEA HOLT, ROB HOLT, RICHARD LAKE, LAURA WAINMAN. STANDING, FROM LEFT: MICHAEL GANIC, SOPHIE SNEDDON, WAYNE ASTON, CAITLIN TILSED, EMMA PORT, RACHAEL ZEMEK.

QIMR-NCARD SYMPOSIUM

A group of Perth NCARD researchers, including Canadian visiting fellow Professor Rob Holt, crossed the country to Brisbane in mid-May for a symposium with their colleagues and counterparts at the Queensland Institute of Medical Research to compare and collaborate on their research in genetic sequencing. Professor Nicola Waddell from QIMR and Professor Jenette Creaney from NCARD constructed a program that covered human and mouse exome sequencing, whole genome sequencing, next generation sequencing, heterogeneity, clinical and meta-analysis, and a comparison of clinical trials in WA and Queensland. Dr Ian Dick and PhD student Sophie Sneddon stayed on at QIMR for several days afterwards to learn the "black magic" of the QIMR research team.

NCARD-QIMR DINNER. FROM LEFT: ROB HOLT, SOPHIE SNEDDON, IAN DICK, JOHN PEARSON (QIMR), NICOLA WADDELL (QIMR), BRUCE ROBINSON, JENETTE CREANEY, ANN-MARIE PATCH (QIMR).

NCARD-QIMR MEETING LINE UP. FROM LEFT: IAN DICK, JENETTE CREANEY, JOHN PEARSON, NICOLA WADDELL, BRUCE ROBINSON, KEN O'BYRNE (TRANSLATIONAL RESEARCH INSTITUTE), ROB HOLT, SOPHIE SNEDDON, ANN-MARIE PATCH.

LEA AND ROB HOLT

It would be too difficult to sum up how rewarding, enriching, productive and just plain fun it was to have Lea and Rob Holt become a part of the NCARD team from January to the start of July, Rob as Visiting Research Fellow, and Lea as an indispensable part of Jenette Creaney's biomarkers team. The family's return to Vancouver by no means signals the end of our connection, although it was a long-awaited opportunity for the world travelling Holts – Rob and Lea and all four children – to reunite.

LEA AND ROB HOLT WITH SOPHIE SNEDDON (CENTRE)

NORWAY BIOMARKERS SYMPOSIUM

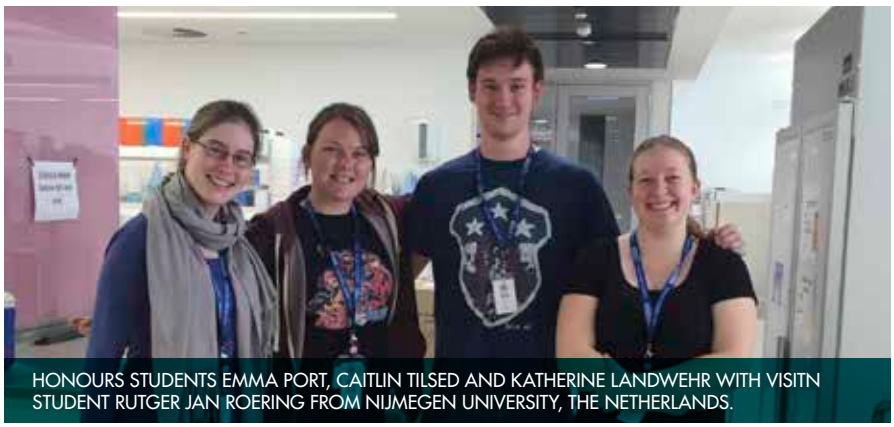
"Trondheim is beautiful at that time of the year as well, green, by the Trondheim fjord and with the midnight sun". Those words would surely be captivating enough, but Jenette Creaney was invited by Oluf Dimitri Røe to speak at the 1st International Symposium on Current and Future Clinical Biomarkers of Cancer at St Olav's Hospital, Trondheim, Norway, 16-17 June, for "the fundamental contribution you have made for the discovery of mesothelin in mesothelioma, and the development of a biomarker and a treatment target, from innovation to implementation". The symposium offered an excellent opportunity for networking and discussing potential collaborations in surroundings as beautiful as promised. But there was more: the conference dinner guests were regaled with traditional Greek music, including Oluf on fiddle and bagpipes, and scientists joined in "Zorba" dancing, while the midnight sun streamed through the windows.

PROF OLUF DIMITRI RØE WITH PROF JIANWEI ZHOU IN BEAUTIFUL TRONDHEIM. (THANK YOU TO PROF JIANWEI ZHOU FROM NANJING UNIVERSITY FOR PHOTOGRAPH).

OLUF DIMITRI RØE PLAYS TRADITIONAL GREEK BAGPIPES WITH THE BAND, TRONDHEIM. (THANK YOU TO ANIMESH SHARMA FOR PHOTOGRAPH).

MESOTHELIOMA PROGNOSIS PAPER

NCARD team members Richard Lake, Anna Nowak and Jenette Creaney recently published a paper with collaborators, including Dr Fraser Brims, which used simple clinical information such as weight loss, routine blood test results, and the type of mesothelioma to allow doctors to better estimate the prognosis for people with mesothelioma. This allows doctors to move away from giving an 'average' prognosis, and to start to better individualise this important information. www.ncbi.nlm.nih.gov/pubmed/26776867 links through to the abstract of this paper.



HONOURS STUDENTS EMMA PORT, CAITLIN TILSED AND KATHERINE LANDWEHR WITH VISITN STUDENT RUTGER JAN ROERING FROM NIJMEGEN UNIVERSITY, THE NETHERLANDS.

RUTGER RETURNS

The apparent tradition of scientific staff and exchange between the Netherlands and Australia continues at NCARD, which hosted Rutger van Röring from Nijmegen University for four months, for study somewhere between an Honours and a Masters. Rutger endeared himself not just with his scientific acumen, but his baking skills, which ensured a return would be welcome.

NEIL WATKINS VISITS NCARD

NCARD was delighted to host a visit from Professor Neil Watkins at the end of May, to discuss research projects and possibilities for collaboration.

A clinician-scientist who holds the Petre Chair in Cancer Biology at the Garvan Institute of Medical Research in Sydney, Neil completed Medicine and a PhD at UWA, before moving to the Kimmel Cancer Centre at Johns Hopkins University in Baltimore to pursue postdoctoral work. On returning to Australia in 2009, he played a key leadership role at Monash University in Melbourne in the strategic plan for cancer research, and in the formation of the Monash Comprehensive Cancer Consortium.

He gave a very well attended presentation as part of the Harry Perkins Institute for Medical Research Lunchtime Seminar Series, entitled: Lung Cancer: all roads lead to platinum, which looked at the issues of carboplatin and cisplatin therapy. Carboplatin can be harmful to bone marrow, and cisplatin can severely affect the kidneys. In treatment for testicular cancer, for instance, measurable renal defects are an ongoing consequence for many young patients.

Neil's team has found very promising results for Follistatin, a hormone that has been known for many years in the field of reproductive medicine. In mouse models it has the potential to both enhance the effectiveness of the platinum treatments, and decrease the side effects. It may also help patients gain weight and muscle mass. Clinical trials testing Follistatin in combination with platinum chemotherapy for the treatment of lung cancer will be commencing at Monash Medical Centre this time next year.

Since moving to the Garvan Institute, which has a strong genomic focus, Neil has taken advantage of the fast and inexpensive genomic sequencing to move his career in a different direction. With clinicians Tracy Leong, Dan Steinfort and one of NCARD's Scientific Advisors, Lou Irving, together with two bioinformatics research specialists Mark Cowley and Velimir Gayevskiy, Neil is exploring the possibilities of Endobronchial Ultrasound Guided Fine Needle Aspiration (otherwise known as EBUS FNA) to remove whole columns of tumour cells from primary tumours. The amount of genetic material that can be collected with this method, compared to the old and very disappointing forceps method, he compared to "a goldmine".

Using these samples to create a genomic map of metastases can provide surprising information about why some tumour sites respond to different treatments, such as chemotherapy or immunotherapy, compared to others. In one particular study of a patient diagnosed with Stage IV Squamous Cell Carcinoma, it demonstrated that one of the metastases was in fact a small cell carcinoma, which could have been developing 10 years before the primary tumour was detectable.

As Neil concluded, these new approaches are an indication of how much more we have to learn and understand about lung cancer.

Drug Discovery at Blue Sky

JOOST LESTERHUIS

Keystone Symposia in Molecular and Cellular Biology is a non-profit organisation based in Colorado that convenes several dozen conferences in the life sciences every year, about half of which are held in mountain areas across the US and Western Canada. Busy researchers and clinicians can thus combine science with skiing. Dr Joost Lesterhuis, who migrated from The Netherlands to work at NCARD, attended the conference "Modern Phenotypic Drug Discovery: Defining the Path Forward" in the US resort of Blue Sky, Montana in May. As Joost pointed out, he comes from "the flattest country in the world": mountain skiing is not one of his skills.

One of the particular problems with mesothelioma is its 'invasiveness'. Normal cells stay within the limits of their tissue: they will never penetrate through local barriers such as membranes or capsules surrounding organs. The fundamental difference between normal cells and cancer cells is that cancer cells no longer stick to those rules. Once they become cancerous, mesothelioma cells start to invade other tissues such as ribs, muscles and blood vessels. This results in symptoms such as shortness of breath and pain. It is not known what makes mesothelioma such an invasive cancer.

In one of our projects we aim to identify the molecular "programs" in mesothelioma cells that play an important role in the invasive growth of mesothelioma, then try to identify and develop drugs that can inhibit that process. This work has recently been funded by a project grant from Cure Cancer and Cancer Australia.

With this project in mind, I attended the conference "Modern Phenotypic Drug Discovery: Defining the Path Forward" at Blue Sky Montana involving participants from top academic institutes and the pharmaceutical industry.

We cannot test drugs in patients before we have some idea whether they will be safe, and whether they will work. We thus always need to first test drugs in disease 'models'. These models are usually cells in culture, or animals with the disease.

What was very clear from several presentations at the Drug Discovery conference is that the quality of the model is crucial for the chance of successfully identifying a drug that will work in patients; much more so than the number of drugs tested. This could have very important consequences for drug discovery in academia and industry.

Traditionally, drug discoverers tend to develop many thousands of drugs for a specific type of cancer and test those on a few cancer cell lines in culture dishes. The evidence now suggests that it may be a lot better to test only a few drugs, but in a (perhaps far more laborious and costly) model that is much closer to the experience for patients. For mesothelioma, for instance, the model would be mice that really develop mesothelioma only after asbestos exposure, as patients do. Or it would be by using a sample of tumour directly cultured from a patient. This was really good to hear, because at NCARD we are already developing these models in our laboratory, which hopefully makes us well placed to identify effective new drugs.

I presented our data and had some very useful discussions. In fact it was one of the best scientific meetings I have ever been to, with excellent presentations, great opportunities to meet with international colleagues with similar interests, and in beautiful surroundings (even if you don't ski).

DNA SEQUENCING FOR DUMMIES

SOPHIE SNEDDON

A number of researchers at NCARD use DNA sequencing to identify mutations in mesothelioma tumours in the hope of successfully targeting them with innovative immunotherapies. Here PhD student Sophie Sneddon explains DNA sequencing.

Our cells contain DNA – a molecule made of bases (A, G, C, T) that when strung together contain the genetic code that enables life. DNA contains information in the form of genes. In a normal, healthy cell, DNA provides the means for the cell to produce everything it needs to function properly. However, if DNA is damaged this can lead to diseases such as cancer. Substances that damage DNA in a way that causes cancer are called carcinogens. The damage caused by carcinogens can result in the DNA acquiring mutations – changes in DNA that can switch on or off genes that help our cells stay healthy.

The project to identify the complete human genome sequence – that is, the entire human genetic code – began in 1988 and took 15 years, $2.7 billion and an international collaborative approach to complete. These days the process is much simpler. Rather than sequence a person's DNA piece by piece, we are now able to break the DNA into smaller pieces of about 100-300 bases long and determine the sequence of millions of these pieces at the same time. Once each piece has been fully sequenced, the pieces are then reassembled back together using highly intuitive computer programs. This process can take place within a day and at a fraction of the cost of the original Human Genome Project.

Only 1% of the human genome contains genes that produce the proteins that function to keep us healthy. This part of the genome is called the exome, and we can sequence only that part to find the mutations that cause changes to proteins that may be linked to disease. By sequencing the exomes of tumour cells as well as normal healthy cells from a patient, we can compare the sequence information to find the potential mutations that have developed specifically in the patient's tumour.

DNA sequencing has become a powerful tool in the fight against cancer. As sequencing quality gets better and the cost becomes cheaper, the possibilities for using this information to target cancer cells increases. What this means for a patient is that it can be possible to quickly identify their specific tumour mutations and determine a possible course of action depending on the mutations driving their cancer. For instance, in some cancers certain mutations are able to be targeted with drugs which can stop cancer in its tracks.

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