WHAT IS SARCOMA?

Sarcomas are rare, devastating cancers that arise anywhere in the body. The two main categories of sarcoma are soft tissue sarcomas, affecting mainly adults, and bone sarcomas, which are much more common in children and young adults. There are more than 50 subtypes of sarcoma that develop in the connective tissues – bone, muscle, tendons, nerves, fat, cartilage and blood vessels – each requiring different treatment and needing highly specialised multidisciplinary care.

SARCOMA RISK FACTORS

In most cases the cause of sarcoma remains unknown. Increased risk includes exposure to radiation and chemical carcinogens – including radiation and chemotherapy for treatment of a previous cancer. But several genetic disorders that run in families can predispose a person to sarcoma. These include Li-Fraumeni syndrome, neurofibromatosis, Gardner syndrome and retinoblastoma. There is also a heightened risk if other family members have had sarcoma.

TREATMENT

Surgery to remove the tumour is important in the treatment of most sarcomas. In osteosarcomas, for example, limb sparing surgery, as opposed to amputation, can now be used in at least 90 per cent of cases. Young patients, however, often need ongoing rehabilitation and a range of expensive prostheses throughout their growing years.

Radiation and chemotherapy also have important roles to play prior to, and after, surgery or may be the main treatment option. Nevertheless, treatment can be long and hard, lasting about a year for many patients. Newer treatments use drugs or man-made versions of antibodies from the immune system to block the growth of cancer cells while leaving normal cells undamaged.

SURVIVING SARCOMA

About 60 per cent of patients diagnosed with a soft tissue sarcoma are cured by surgery with or without radiotherapy, if the cancer has not spread to other parts of the body. Cure rates are much lower once sarcomas have spread to other sites. The survival rate for bone sarcomas is about 70 per cent if the cancer has not spread and surgery is vital if the cancer is to be cured. However, chemotherapy is used for the most common subtypes of bone sarcomas – Ewing sarcoma and osteosarcoma – and, along with surgery, is critical to curing the patient.

One in five sarcoma survivors will develop a second cancer, including a second sarcoma, within 10 years. Radiation therapy itself can be a risk factor for a recurrence. Even though patients are monitored closely the risk of recurrence is a great source of anxiety for patients and their families and is devastating when it happens.

Did you know?

- Sarcoma accounts for around 1 per cent of all cancers, but up to 20 per cent of cancers in children and up to 10 per cent in young adults.
- Two in five patients with sarcoma will go on to die from their disease.
- As sarcoma affects a younger population, it contributes a disproportionately heavy burden on the community over the term of their lives.
- One in five sarcoma survivors will go on to develop a second cancer within 10 years.

Identifying those at increased risk may lead to early detection, more effective treatment and better survival. This is why the Garvan’s Professor David Thomas is searching for new ways to predict who is at increased risk and what individualised therapies and surveillance might offer the best outcomes.

GARVAN – A WORLD CLASS CENTRE FOR SARCOMA RESEARCH

Garvan’s sarcoma research is diverse. To understand why some people get sarcomas, Professor Thomas created the International Sarcoma Kindred Study (ISKS), the largest study of inherited sarcoma risk ever undertaken globally. Early results have shown how two or more rare genetic mutations can dramatically increase a person’s cancer risk. This means that at-risk people and their families can potentially be identified earlier and receive tailored care.

The second wave of this research, the Surveillance in Multi-Organ Cancer prone syndromes (SMOC+) study, is following up people identified as being at increased cancer risk and offering tailored cancer surveillance and risk management.

Finally, the Molecular Screening and Therapeutics (MoST) program is a set of clinical trials tailored for people with rare and neglected cancers in general, which will benefit people with sarcomas.

WORLD FIRST WHOLE GENOME SEQUENCING OF SARCOMA

The Garvan Institute recently became one of the first in the world to acquire technology that can sequence a whole human genome at a base cost of around US$1000. This will give Professor Thomas and his team the unprecedented ability to undertake whole genome sequencing on the 3000 families in the ISKS study.
International Sarcoma Kindred Study Collaborators

- Asan Medical Center, Seoul, Korea
- Centre Georges François Leclerc, Dijon, France
- Centre Régional de Lutte Contre le Cancer Léon Bérard, Lyon, France
- Centre Régional de Lutte Contre le Cancer Oscar Lambret, Lille, France
- Chris O’Brien Lifehouse, Sydney, Australia
- Christchurch Hospital, Christchurch, New Zealand
- Derriford Hospital, Plymouth, UK
- Garvan Institute of Medical Research, Sydney, Australia
- Hollywood Private Hospital, Perth, Australia
- Hospitaux de Marseille, Marseille, France
- Huntsman Cancer Institute, University of Utah, Utah, USA
- Institut Gustave Roussy, Villejuif, France
- Mt Sinai Hospital, New York, USA
- Peter MacCallum Cancer Centre, Melbourne, Australia
- Prince of Wales Hospital, Sydney, Australia
- Princess Alexandra Hospital, Brisbane, Australia
- Royal Adelaide Hospital, Adelaide, Australia
- Royal Liverpool and Broadgreen University Hospital, Liverpool, UK
- Royal Marsden Hospital, London, UK
- Royal Prince Alfred Hospital, Melbourne, Australia
- Tata Memorial Hospital, Mumbai, India
- University College London Hospital, London, UK
SARCOMAS DON’T HAPPEN BY ACCIDENT

We now understand that there are significant familial risk factors for sarcoma and Garvan’s Professor David Thomas and his team are examining the family links and genetic predisposition to sarcomas and offering the chance to access new therapies via the Molecular Screening and Therapeutics (MoST) clinical trials program.

Professor David Thomas is the Director of The Kinghorn Cancer Centre, as well as Head of Garvan’s Cancer Division. The Kinghorn Cancer Centre is a joint venture of Garvan and St Vincent’s Hospital that brings together the scientific and medical expertise of the two partners to provide a personalised medicine approach to the treatment and care of cancer patients.

‘My interest in sarcomas extends from genomic research within tumours, all the way through to clinical trials,’ explained Professor Thomas.

‘My lab focuses on the genetics of sarcomas, as well as cancers more broadly in young adults. We use patient-centred approaches to understanding human disease, complemented with cellular and animal models to explore biological processes relevant to cancer.

‘Because hereditary predisposition is a key risk factor for sarcoma, we have created a large informative group of patients and families affected by cancer, and are applying state-of-the-art genomic technologies to understand the basic question: “Why me?”

‘More recently, we have become interested in developing innovative strategies to translate our research insights into tools and treatments to help patients and their families.’

Personalised medicine

Professor Thomas feels that this is a critical time for the development of personalised medicine and the use of genomics in clinical care. ‘Cancer treatments have traditionally been very toxic and may have life-long consequences. There is no point in using treatments that won’t work and may cause harm,’ he said.

‘And all too often, we detect cancers too late to cure them. It is important that we use the right drug in the right person; and also that we understand who is at risk of cancer, so we can direct our efforts towards early detection in the most effective way, particularly in the young, where cancer is so rarely suspected.’

Unlike the more common and well-studied cancers like breast, bowel, lung or melanoma, rare and neglected cancers, like sarcomas, often don’t have well-defined treatments. ‘Because sarcomas are understudied, there simply isn’t the evidence-base for treatment, which means that we need to tailor treatment for each individual – and if we can’t do this, we are often left without accepted or effective therapeutic options,’ said Professor Thomas.

Genomics information can be used to guide treatments, estimate the risk of relapse, make reproductive choices and define surveillance for second cancers. It can also be used to pick up cancers in apparently unaffected family members.

The International Sarcoma Kindred Study

The International Sarcoma Kindred Study (ISKS) is an Australian initiative investigating the heritable aspects of adult-onset sarcoma. Recruitment began at six sites in Australia in 2009 and has since expanded to 21 sites globally, including in France, India, New Zealand, USA, UK and Korea, with the global study centre in Australia as a biospecimen storage facility, laboratory and database repository.

Sarcoma patients and their families are asked to complete a family pedigree and questionnaire and give blood samples. There are more than 1700 families involved worldwide, with recruitment aiming for 3000 families internationally.

To date more than 1000 individuals with sarcoma have been screened and the researchers have uncovered numerous new genetic risk factors for the cancer – and, in a world first for any cancer type, they showed how carrying two or more of these rare mutations increases an individual’s cancer risk.

The ISKS team looked at a ‘gene panel’ of 72 genes in each participant. They identified a number of new genes that significantly increase the risk of developing sarcoma, including mutations in the genes ERCC2, ATR, BRCA2 and ATM. Importantly, in individuals carrying mutations in two
At the age of 11, Luke Ryan was diagnosed with an osteogenic sarcoma growing from the back of his left knee. He remembers the treatment as ‘A lot, a long time and just beyond horrendous’. He had 12 months of chemotherapy with five different agents during three-to-five-day hospital stays with a week-and-a-half break between each one. ‘Three months in, I had a seven-hour limb salvage operation that left me with a full knee replacement, a slight leg extension and half a dead person's femur, and without most of my quads,’ said Luke. ‘It was not fun.’

Even in a close and comparatively well-off family, Luke says it’s hard to overstate how tough that year was for everyone. ‘Mum became my full-time carer, in hospital with me from morning until night. Dad would split his time between the hospital he worked at and the hospital where I was being treated, and my brother, who had just begun Year 12, was essentially abandoned in the middle of the most important year of his life. Still, we survived, because that’s what you do, and our bonds were only strengthened in the face of such hardship.’

As Luke had essentially missed the first year of high school, by the time he returned to school it was hard for him to be a part of the groups which had formed in his absence. ‘It was certainly very difficult for a while,’ he recalls, ‘and I remained a peripheral figure for the rest of my schooling because of it. Fortunately my great passions were reading and video games, so they were easy enough to pursue, even absent full use of my leg.’

Following treatment, Luke was monitored for five years and then the month before he finished school, his doctors told him he was cured. ‘I cried when they told me I was done, although I can’t quite remember why. It didn’t feel like joy, just survival.’

Managing increased risk
Understanding inherited risk is clinically important for several reasons. Many sarcoma patients are in their reproductive years and effective strategies now exist for antenatal and pre-gestational diagnosis if a cancer predisposition gene is identified.

As ionising radiation increases cancer risks, it is important to avoid diagnostic and therapeutic radiation exposure in high-risk individuals where mutations are identified and it is possible to do so without compromising care.

Taken together, the pace of recent developments in genomic screening programs suggests that the issue of genetic testing and management will become an increasingly important area for research.

‘We are moving from the ISKS to a new generation of cancer risk management with the world first Surveillance in Multi-Organ Cancer+ (SMOC+) study that looks at families carrying an excess of genetic risk over an extended period of time.

‘Our goal is to recruit 3,000 families with sarcoma to the ISKS and then to undertake whole genome sequencing of these individuals, to map comprehensively the genetic basis of developing these rare diseases of the young.

‘Until now, we’ve been limited to single-gene thinking, so we tell patients, for instance, that carrying a BRCA1 mutation means your breast cancer risk is higher, or that your risk of sarcoma and other cancers is higher because you’ve got a particular p53 mutation.

‘The study shows us that the landscape of cancer risk is far more complex than that. We can now see that the risk for developing sarcoma is equally due to the combined effect of multiple genes, and that the more mutations you carry, the earlier the onset of cancer.

‘These previously invisible effects are at least as large as the impact of a mutation in p53 itself, currently the strongest known genetic cause of sarcoma. Being able to identify these at-risk individuals, and their families, means that we can manage risk better and help those people to get the care they need, when they need it.

‘Understanding the genetic drivers that give a person an increased risk of cancer also helps us understand how best to treat that person’s cancer. And for about a third of the individuals we studied, the gene mutations they carry have implications for how they should be treated.

‘A lot of what we’re doing going forward is looking at how we use genetic information about risk to alter the way we treat people. The more we know, the more precisely we can match individuals with the best possible treatment for them.’
Luke Ryan – Aged 22

Luke Ryan was 22 when he was diagnosed with sarcoma for the second time – in his right arm. He had just finished an arts honours degree at Melbourne University and was part way through a second degree in law. ‘I was diagnosed on a Saturday night and by Monday morning I had been wrenched out of my cosy existence and forced to move back to the family home in Perth,’ said Luke. ‘Suffice to say, I was less than enthused by this turn of events.’

This time, however, the treatment was much easier to tolerate with two nine-week batches of chemotherapy and six weeks of radiotherapy. Three to five days in hospital became two to three hours. ‘I was energetic, healthy and for the first time in months no longer crippled with pain. Chemotherapy made me feel substantially better than I did before. It was really something.’

Surgery was supposed to be part of the regimen, but the only possible option was a forequarter amputation of Luke’s right arm and was something that he simply couldn’t face.

Luke has been clear of sarcoma for seven years now and there are plans for his monitoring to be wound down. ‘It was a conversation we spent a long time thinking we might never be able to have,’ said Luke. ‘The future is wide open. I’m happy, my life is full of friends and laughter and I make almost no concessions to my past illnesses. As a stand-up comedian and writer I’ve even built a fair career out of what happened to me in 1997 and 2007. Now though, I’d like to start talking about something else.’

Receiving a rare cancer diagnosis not once, but twice, has made Luke acutely aware of the importance of medical research. ‘The change in treatment methodologies between my two tumours and the impact that had on my lived experience cannot be overstated – in the first, an intolerable barrage of crippling chemotherapy that almost killed me. In the second, a well-measured regime that allowed me to continue on with my life largely unchanged,’ said Luke. ‘That happened in just 11 years. Incredible things can be achieved, so long as we continue to work towards them.’

‘So far, SMOC+ has delivered important information for family members who don’t yet have cancer. In clinical practice, screening BRCA1 carriers reveals a rate of asymptomatic cancer of 2 women for every 100 screened. In the SMOC+ study to date, of 27 at-risk individuals screened, 3 were found to have asymptomatic but curable high-grade cancers. SMOC+ is showing that information about genetic risk can be used to offer personalised surveillance that could save lives.

The Future of Genomic Cancer Medicine

‘Neglected and understudied illnesses, such as sarcoma, have such devastating impacts because not only do they comprise more than 1 in 5 cancers, but they are more lethal than most cancers, representing 1 in 3 cancer deaths. They are neglected because they are individually rare, but taken together they comprise a major health challenge. The good news is that I believe neglected cancers offer the greatest opportunities for breakthroughs, precisely because they have not been studied in as much detail. These approaches offer greater possibilities of early detection and better treatment, as well as novel clinical trials that will increase access by cancer patients to new therapies.

The MoST program is tailored for people with rare and neglected cancers in general and will benefit people with sarcomas. In the MoST trial, we offer tumour testing and treatments for people with no other options. Using genomics, we test the tumours and target those mutations with drugs and other targeted therapies. The SMOC+ study looks at cancer risks and surveillance, and with MoST we have new clinical treatments.

The MoST program will evaluate the effectiveness of new treatments using an innovative clinical trial design where patients will undergo molecular screening and then be assigned to substudies of targeted therapies based on specific genetic alterations. The program includes an immunotherapy substudy open to patients who cannot be matched with a targeted treatment.

‘It is important to bring genomics into clinical care. We need to translate fundamental scientific knowledge into interventions that help patients – to assess cancer risk or to evaluate molecular targeted therapies.’
Throughout its more than 50-year history, Garvan researchers have been responsible for significant breakthroughs that have improved our understanding and the lives of people living with some of the most common, yet complex diseases affecting society today.

These include:

- Sarcoma
- Hearing loss
- Cancer
- Lupus
- Obesity
- Alzheimer’s disease
- Osteoporosis
- Parkinson’s disease
- Arthritis
- Asthma

We are currently in the midst of the genomic revolution – using the information contained in an individual’s DNA to understand the basis of human development, help evaluate the genetic risk of disease, predict outcomes, and determine the most effective treatments for that individual.

I am proud to say that Garvan is one of the leading institutes internationally in the development and application of new genomic technologies to understand human disease and its prevention and treatment. The acquisition of the most advanced sequencing technology in the world has positioned Garvan as the human genomics hub for Australia and the region. It allows massive increases in genome sequencing capacity, accelerating medical research across the spectrum to include cancer, osteoporosis, autoimmune diseases, diabetes and neurological diseases.

Given Garvan’s exceptional research talent, combined with its innovative use of leading-edge technology, I am excited by the potential of our work to deliver real benefits to this generation and those to come.

Professor John Mattick AO FAA
Executive Director
Garvan Institute of Medical Research

To sustain Garvan research projects, the Garvan Research Foundation aims to match government funding dollar for dollar.

Philanthropic support not only alleviates some of the financial stress on research teams, it also encourages innovation. It is vital for funding promising novel projects that do not yet have enough basic data behind them to be eligible for government funding.

Donations are also crucial for the purchase of the equipment and technology that is essential to modern day medical research, but is not eligible for government funding.

Your donation can help support these cutting-edge projects and purchase vital equipment to continue achieving life-changing breakthroughs.

Andrew Giles
Chief Executive
Garvan Research Foundation

WHY INVEST IN GARVAN’S SARCOMA RESEARCH?

- Find breakthroughs in our understanding of sarcoma
- Lead to new sarcoma treatments
- Lead to new ways to predict sarcoma in families
- Reduce the impact of sarcoma on the Australian community

For information about how you can help Garvan’s sarcoma researchers improve outcomes for the children and young adults living with this disease today, as well as future generations, contact:

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Front cover images:
Top: Chromosomal abnormalities in liposarcoma. Each normal chromosome pair has its own colour. The multicoloured structures attached to chromosomes 4 and 5 harbour dozens of copies of cancer-causing genes MDM2 and CDK4, which drive liposarcoma growth. Courtesy Professor David Thomas.
Bottom left: Researcher Dr Mandy Ballinger tracking enrolment and participation in the International Sarcoma Kindred Study.
Bottom right: Sarcoma patient.