Nicole Cloonan

Towards Personalized Medical Genomics

Cancer is Australia's largest disease burden, and arises as from the accumulation of genetic damage. This damage comes in many forms including: (i) mutations that alter or destroy the function of important genes; (ii) mutations that alter chromosome structure through insertions, deletions, rearrangements and/or amplifications; (iii) direct modification of the DNA which affects the regulation of genes (methylation); (iv) the disruption of protein scaffolds that organize DNA structure (chromatin); and finally (v) mutations leading to the inappropriate activation or silencing of important genes. Typically cancers accumulate multiple mutations, and these will vary from one cancer type to another, from person to person, and may even vary between different tumour sites in the same person. This variation could mean the best treatment for one patient might have no effect for another, or that a treatment that worked in the past might have no effect upon on a cancer relapse.

The ultimate dream for cancer patients would be to determine exactly what mutations caused the disease, and exactly what treatments would work the best – a concept known as personalized medical genomics. Our research is rapidly turning this dream into an achievable and affordable reality. Using cutting edge technology and world leading research techniques we now have the ability to determine the full repertoire of genetic mutations within a cancer – and this is giving us new biological insight, and new avenues for both diagnostics and therapeutics.

High-Throughput Sequencing Of The Molecular Events In Cancer

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The ideal way to characterize both the genomes and the transcriptomes of tumour samples with the highest possible resolution is to determine the sequence of all DNA and all expressed RNA within the same sample. High-throughput sequencing has enabled 'RNA sequencing' (RNAseq – via random cDNA libraries) – a method to survey the content and dynamics of the transcriptome at single-nucleotide resolution. The same technology has also been applied to rapidly and accurately determine the total genomic and epigenomic content of model systems, including structural and sequence variations, and we are on the verge of a revolution within the field of genomics. Integration of these "omic" data sets gives us unprecedented power and resolution with which to study the biology of cell states and diseases, allowing genuine systems-biology approaches to be utilized.

We have completed pilot studies of tumors and transformed cell lines where we have sequenced the DNA, RNA, and miRNA content of these cells. Genomic DNA has been sequenced using a "mate-pair" strategy (also known as "di-tag" or "paired-end"), where each end of a DNA fragment is captured and sequenced. The alignment of these sequences to a normal or reference genome allows us to identify structural variations (insertions, deletions, translocations, amplifications, and inversions), as well as sequence content variations (SNPs, MNPs, etc). We have identified and characterized the transcriptional output (including mRNA, ncRNA, miRNA, and other small RNAs) from these samples using a strand-specific library generation protocol. Data and information management for such large scale projects is critical, and we have designed and developed an efficient computational pipeline that integrates analysis and visualization – and this has been tested on >200Gb of transcriptomic and genomic data. We have developed customized software for the identification of genomic variants and transcriptional output from every locus, allowing us to survey and integrate data from mRNA expression, microRNA activity (known and novel), repetitive elements, SNPs, RNA editing events, and structural variants. These data sets will allow the development of the first genuine systems-biology models of cancer development and progression – and this integrated approach has already given us a greater understanding of key biological processes (such as the regulation of the cell cycle). Together, these approaches pave the way not just for personalized medical genomics in Australia, but will accelerate both novel biomarker discovery, and the development of novel therapeutic approaches

Research in lymphatic vessels biology and relevance in novel cancer treatment

Lymphatic vessels are a vital component of the cardiovascular system and serve several functions critical for fetal development and adult health, such as collecting fluids from the tissues and transporting immune cells. We have identified a gene *(Sox18)* that controls the mechanism by which lymphatic vessels develop in the embryo. Understanding how lymphatic vessels grow in the embryo is crucial because the reactivation of lymphatic vessel growth in adults is the mechanism that enables tumours to spread. Our discovery provides solid ground to develop new ways that will improve cancer treatments by preventing cancer cells from colonising the body. This work has been recently published in the top ranking scientific journal *Nature* (François et al, *Nature,* Dec 2008)

Outcomes

The recent discovery of the pivotal role of *Sox18* in lymphatic biology is crucial because it will allow clearer understanding of how lymphatic vessels are reconstructed during onset of diseases. Cancer remains one of the main causes of death in the world (12 million new cases diagnosed and 7 million deaths per year globally). Our discovery is relevant to the field of cancer research because it will enable researchers to control the growth of lymphatic vessels during tumour progression in order to prevent cancer cells from spreading.

Some 30% of breast cancer patients are afflicted with secondary lymphedema, accumulation of fluids in tissues that provokes swelling, pain and disability, following surgical treatment. Our findings are also crucial to develop a new approach that will improve management of secondary lymphedema by promoting re-growth of functional lymphatic vessels, which will allow fluid to drain.

Significance

Biological significance: Very little is understood about the development of the lymphatic vasculature. Our project has produced important new knowledge about how lymphatic vessel growth is controlled during development of the embryo.

Medical significance: Abnormal growth of new lymphatic vessels is associated with a wide variety of diseases including secondary lymphedema, inflammatory diseases, obesity and cancer. As a consequence, it is vital to understand how lymphatic vessels develop normally in order to comprehend what molecular mechanism is impaired and causes abnormal development of these vessels.

Innovation: Our discovery lead to the idea of complementing existing anti-cancer strategies based on the blockade of blood vessel development, with treatment that will prevent new lymphatic vessels from forming in order to stop spreading of cancer cells.

Brian McEvoy

What's Past is Prologue
The impact of recent human evolution on gene mapping

Understanding how and why DNA differs between human populations is crucial to finding the many genes that cause complex diseases like diabetes and various types of cancer. Looking for DNA changes that are more common in people with a disease ('cases') versus those without ('controls') is one common approach to finding the genes involved. However, if the genetic ancestry of the cases and controls is also different, then there is a risk of picking out extra genes that have no real role in the disease. Secondly, if the genes for the same disease are different between two populations, then we could miss finding them by combining people of different ancestry. We looked in detail at the ancestry of some Northern European populations- including the Irish, British and Dutch -using hundreds of thousand of changes in their DNA sequences. Even though they are closely related, the ancestry differences between these populations are still great enough to hurt our chances of finding genes and this needs be to be taken into account in gene mapping experiments.

While different ancestries and population histories can interfere with one form of gene mapping, they also make another gene discovery route possible. Under natural selection, versions of a gene that give an advantage in the environment will become more common, while the others will go extinct. Natural selection leaves tell-tale signals in our DNA. Genes that show its effects are likely to have important functions and are good candidates for explaining disease risk. A scan of the Northern European genome, found that immune genes, involved in protecting the body from disease, showed signals of selection probably driven by generations of past infectious epidemics like the infamous 'Black Death' plaque of the 13th century. The modern gene pool is a product of our evolutionary past. Appreciating these past events and their present day genetic legacy will be a significant aid to finding the genetic basis of diseases and fully understanding why it is so complex

Human population stratification - or differences in genetic diversity between geographic groups- presents challenges and opportunities in the ongoing search for the genes that underlie disease and other complex traits. Recognising and correcting for population stratification is a practical concern in gene mapping by many association methodologies. A mismatch in the ancestry of case and control individuals can lead to false positives associations and/or reduced power if the genes that cause a phenotypically similar condition are different across populations. On the other hand, genomic signals of natural selection across populations have the potential to flag genes of exceptional functional importance that are strong candidates to contribute to disease risk. We sought to investigate population structure and diversity over a small region that may be considered genetically homogenous.

Principal component (PC) analysis was used to summarise the major genetic trends present across ~300,000 autosomal single nucleotide polymorphisms (SNPs) in 2099 individuals from populations of Northern European origin (Ireland, UK, Netherlands, Denmark, Sweden, Finland, European-Australia and European-American). The major trends (PC1 and PC2) demonstrate obvious geographic substructure, even over a small area like the British Isles. This observation points to the need to account for population stratification when using individuals with these ancestries in a case/control gene mapping study. For example we can show that with 500 cases from Ireland and 500 controls from neighbouring Britain, there will still be substantial numbers of false positive associations. As sample sizes are increased in the future to detect disease DNA variants of smaller effects so it will become more important to consider even subtle stratification.

While most of the observed differentiation between these populations is due to random genetic drift and the effect of migration, we also detected evidence for the impact of natural selection. This is somewhat surprising given the populations have a relatively similar climatic and ecological environment. However, the selection signal was focused on genes involved in immunity and defense. Variability in the geographic extent of infectious disease outbreaks as well as potentially strong selection coefficients associated with such epidemics are a simple means by which selection could have a detectable effect given other environmental similarities.
The selective action of one specific epidemic may explain the presence of a large region of reduced genetic diversity (a selective sweep) extending over an 8 million base-pair region surrounding the *HLA-G* gene on chromosome 6. The role of the *HLA-G* gene, one of the Human Leukocyte antigen class I heavy chain paralogues, in activating the immune system in response to pathogens, is consistent with infectious disease as the environmental selection force. Historical candidates for this event include the 13th century 'Black Death' bubonic plaque. The selective sweep region also contains loci that are associated with multiple sclerosis and schizophrenia risk. While these disorders are likely to be highly complex, some of the risk may be an evolutionary hangover of selection in response to a long past ancestral health risk.

Overall the results highlight the present day legacy of the recent population past both in understanding and explaining disease risk/prevalence and finding the genes responsible for these complex disease traits.

Glen Boyle

MIC-1 - A new diagnostic marker and therapeutic target for metastatic melanoma?

Glen M. Boyle, Julie Pedley, Adam C. Martyn, Kelly J. Banducci, Geoffrey M. Strutton, David A. Brown, Samuel N. Breit, and Peter G. Parsons.

The incidence of malignant melanoma in Australia has increased dramatically over the past three decades. It is now the third most commonly diagnosed cancer in Australians. Over 1,270 Australians died as a direct result of melanoma in 2004. The survival rate of patients following surgical removal of small primary tumours (less than 1 mm thick) is very good, with over 90% of patients alive five years after diagnosis. Metastatic melanoma on the other hand has an extraordinarily poor survival rate as there is currently no effective treatment; only 11% of patients are alive after five years. Most patients with metastatic melanoma survive from 4 to 6 months. New strategies for the treatment of metastatic melanoma are urgently needed. There is also a need to identify the patients with melanoma that are at a high risk of developing metastases. Using this information, it would be possible to identify those patients requiring immediate aggressive therapy or close monitoring. Unfortunately, no such tests are currently available.

We have identified a gene product called MIC-1, which is not found in the normal cells that go on to form melanoma (called melanocytes), but is present in over half of primary melanomas at low levels. Importantly, this product is found in all metastatic melanoma biopsies we have examined, in very high levels. We have shown that the MIC-1 protein is controlled by a factor known to be altered in melanoma. Removal of the MIC-1 protein from metastatic melanoma cells makes them less able to invade the surrounding tissue, and more susceptible to attack by the immune system.

This melanoma marker protein is known to be shed into the blood stream. This protein could therefore serve as a blood test to detect and manage melanoma patients. It may also be a good drug target for the treatment of metastatic melanoma.

The incidence of malignant melanoma in Australia has increased dramatically over the past three decades. It is now the third most commonly diagnosed cancer in Australians. Over 1,270 Australians died as a direct result of melanoma in 2004. Five year survival of patients following surgical removal of primary tumours less than 1 mm thick is very good, at around 93%. Metastatic melanoma on the other hand has an extraordinarily poor survival rate as there is currently no effective treatment. Five year survival of patients with metastatic disease is only 11%, with the median survival only 4 to 6 months. New strategies for treatment of metastatic melanoma are urgently needed. There is also a need for better predictive markers capable of identifying primary lesions with enhanced metastatic potential. These markers could identify patients requiring early aggressive adjuvant therapy or close monitoring. No such markers are currently available.

We originally identified a gene encoding Macrophage Inhibitory Cytokine (MIC)-1, that is highly expressed in melanoma cell lines when compared to cultured normal primary human melanocytes. MIC-1 is a divergent member of the TGF-β superfamily. Expression of MIC-1 is dramatically increased in acute injury, inflammation and many cancers, including prostate, breast, colon and pancreatic cancer. Of 53 melanoma cell lines that were examined for relative MIC-1 expression by western blot analysis, 35 (66%) showed significantly higher levels of MIC-1 compared to normal melanocytes. We found that MIC-1 is not expressed in normal melanocytes or naevi from patient biopsies, but present in over 50% of primary melanoma biopsies at low levels (15/22). Strikingly, we observed very high expression of MIC-1 in all metastatic melanoma biopsies we examined (16/16). Using chromatin immunoprecipitation (ChIP) assays, we showed that MIC-1 is controlled by the lineage-specific melanoma oncogene, the microphthalmia-associated transcription factor (MITF). Pharmacological inhibitor studies showed that this expression is downstream of the MEK1/2 / ERK1/2 and PI3-K / Akt pathways.

We found that MIC-1 is required for tumour growth of human melanoma cells in a mouse model. Knockdown of MIC-1 expression using stable short-hairpin RNA in three melanoma cell lines showed a significant decrease in tumorigenicity in athymic mice ($p<0.0001$). These results suggest that MIC-1 promotes melanoma development and may be a target for the treatment of metastatic melanoma. Our latest data suggests that MIC-1 may have suppressive effects on cells of the immune system, as well as signalling effects in the melanoma cells. MIC-1-ablated tumour cells were rapidly cleared following subcutaneous injection in athymic mice. Further, ablation of MIC-1 in the highest expressing melanoma cell lines leads to a reduction in phosphorylation levels of ERK1/2.

These results indicate that MIC-1 may function to promote development of more aggressive melanoma tumors. MIC-1 is a secreted protein, and therefore could be developed as a blood test for detection and management of metastatic melanoma. MIC-1 may be suitable for development as a possible target for the treatment of metastatic melanoma.

Patricia Valery

Education intervention for childhood asthma by Indigenous Health Workers in the Torres Strait

Indigenous children in the Torres Strait have more severe asthma than mainland non-Indigenous children and the parental knowledge of asthma there is poor. As involvement of Indigenous health-care workers in asthma programs seemed likely to be beneficial, we conducted a randomised controlled trial in this region to examine the benefits of an education intervention, delivered by local Indigenous health-care workers.

Eighty-eight children diagnosed asthma were, by chance, allocated to receive either three additional asthma education sessions with a trained Indigenous health-care worker (35 children) or no additional education (53 children).

We found that this education intervention improved some, but not all, asthma outcomes measured in the study. Carers in the intervention group were significantly better in the 'knowledge of asthma medication' and the possession of and ability to interpret their child's 'asthma action plan'. Also, children who received the education intervention missed fewer school days due to wheezing. However, there was no difference between groups in the main study measure, namely doctor visits for wheezing ('asthma attacks'). When we compared the study measures 'before intervention' (one year before the study) with 'after intervention', we found an improvement in all asthma outcomes that were measured.

Delivery of a community-based asthma education program that includes trained Indigenous health-care workers, improves outcomes for Indigenous children who have asthma. Our findings provide strong support for the effectiveness of a culturally tailored asthma education program for Indigenous children with this condition. Interventions such at this could significantly benefit rural communities at the national level.

Education intervention for childhood asthma by Indigenous Health Workers in the Torres Strait

PC Valery, IB Masters, B Taylor, PO'Rourke, Y Laifoo, AB Chang

Indigenous Australians have higher asthma-related mortality and morbidity than other Australians. In the Torres Strait region in particular, the prevalence of childhood asthma is high with 30% having persistent asthma, as well as parental asthma knowledge being poor. Education is advocated as an essential component in major asthma guidelines to reduce asthma morbidity and mortality. Patient asthma education includes information on medications, their mechanisms of action, appropriate technique for using delivery devices and plans for responding to changes in asthma symptoms (written asthma action plan). We conducted a randomised controlled trial in the Torres Strait region to examine the benefits of an education intervention by Indigenous health-care workers on childhood asthma outcomes.

Methods: Children with asthma diagnosed by a paediatric respiratory physician were enrolled and randomly allocated to: three additional asthma education sessions with a trained Indigenous health-care worker or no additional education, and re-assessed at 12 months. Primary endpoint was the difference in the number of unscheduled hospital/doctor visits due to asthma exacerbation between the groups. Secondary outcomes were improvement of quality of life and functional severity scores, asthma knowledge, interpretability of asthma action plans and school days missed due to wheezing.

Findings: We enrolled and followed up 88 children (81%) aged 1-17 years, 97% Aboriginal and/or Torres Strait Islanders (35 intervention; 53 controls). The groups were mostly comparable at baseline (except for asthma severity which was adjusted for in the analysis). There were no significant differences ($p=0.25$) in the number of unscheduled hospital/doctor visits due to asthma exacerbation (intervention group median=1.0, control group median=0.0). Compared to the control group, carers in the intervention group were significantly better in knowledge of asthma medication ($p<0.05$), possession of ($p=0.01$) and ability to interpret asthma action plans ($p=0.02$). Children in the intervention group missed fewer school days due to wheezing ($p=0.04$) compared to the control group. Both groups improved in quality of life and functional severity scores (baseline vs. follow up) but there were no significant differences between the intervention and control groups.
Interpretation: Delivery of a community-based asthma program that includes trained Indigenous health-care workers improves asthma outcomes in Indigenous children with asthma. Our findings provide empirical support for the effectiveness of a culturally tailored asthma education program for Indigenous children with asthma. Such a model of service delivery can significantly benefit rural communities at the national level.

Kate Markey

Conventional Dendritic Cells Are The Critical Donor Apc Presenting Alloantigen After Bone Marrow Transplantation

KA Markey, T Banovic, RD Kuns1, NC Raffelt, SD Olver, YA Wilson, AR Pettit, JS Bromberg, GR Hill1,and KPA MacDonald.

Bone marrow transplantation (BMT) is the only available curative therapy for many blood cancers such as leukaemia. Graft-versus-host disease (GVHD) occurs after BMT and is a major cause of transplant-related death. GVHD occurs when a white cell called a T cell from the donor transplant attacks recipient tissues in a "rejection" process. Increasing the understanding of how GVHD occurs is critical for the design of new therapies to improve survival in patients undergoing BMT.

Recent work in our laboratory has identified two important pathways which modify GVHD post-transplant. Firstly, we have identified the main cell type, called a "conventional dendritic cell" that is responsible for instructing donor T cells to attack host tissue. Secondly, we have demonstrated that another type of white blood cell, the B cell, can act to decrease T cell activation. Therefore, the development of therapies that a) eliminate the conventional dendritic cell population and/or b) promote an increase in B cells would reduce the extent to which donor cells damage host tissue post-BMT, and could therefore lead to significant improvements in patient outcome.

Bone marrow transplant patients represent one population in whom these therapies would be useful, however in addition, recipients of donated solid organs may benefit, as there are many similarities between solid organ (e.g. kidney) rejection and GVHD.

Conventional Dendritic Cells Are The Critical Donor Apc Presenting Alloantigen After Bone Marrow Transplantation

The ability of donor T cells to respond to host alloantigen (alloAg) following bone marrow transplantation (BMT) leads to graft-versus-host disease (GVHD), a cause of considerable transplant-related mortality. Donor antigen presenting cells (APC) propagate GVHD via the presentation of alloAg within MHC class II to donor CD^4+ T cells. To date the relative contributions of donor APC subsets to alloAg presentation remains unknown.

We have, for the first time, generated transplant systems to investigate donor APC subsets after BMT using the B6 ($I\text{-}A^b/I\text{-}E^{-/-}$) to BALB/c ($I\text{-}A^d/I\text{-}E^d$) model. We first used transgenic (Tg) B6 donor mice in which the diphtheria toxin (DT) receptor is driven off the CD11c promoter, such that donor conventional dendritic cells (cDC) could be specifically depleted after BMT via the administration of DT. CFSE labeled TEa T cells (which possess a TCR specific for host-derived $I\text{-}E^d$ class II peptide, presented only within donor class II ($I\text{-}A^b$)) were subsequently adoptively transferred and alloAg presentation by donor APC quantified by analysis of CFSE dilution. The presentation of alloAg was significantly decreased in the absence of donor cDC (proliferation index (PI): 4.3 ± 0.7 vs. 12.4 ± 2.2, cDC deplete vs. replete; P=0.001). The specific depletion of donor pDC with 120G8 antibody had no effect (PI: 11.2 ± 1.9 vs. 12.4 ± 2.2, pDC deplete vs. replete; P= 0.6). Additionally, the depletion of both donor cDC and pDC did not further diminish the presentation of alloAg relative to animals in which only cDC were depleted. To address the role of donor macrophages in alloAg presentation we utilized B6.MAFIA Tg donors, in which administration of the AP20187 toxin leads to conditional depletion of CSF-1R+ cells (macrophage and DC lineages). Surprisingly, donor macrophages were not engaged in alloAg presentation since the depletion of both populations reduced presentation to the same levels as cDC depletion alone (PI: 4.3 ± 0.7 vs. 5.1 ± 0.9, cDC deplete vs. cDC/ macrophage deplete; P= 0.29). Finally, we demonstrate that donor B cells play a regulatory role since alloAg presentation was increased when B cell deficient grafts were used (PI: 22.7 ± 3.2 vs. 12.4 ± 2.2, B cell deplete vs. replete; P= 0.02).

The identification of the key population driving alloreactivity has major implications for the design of therapeutic strategies post-BMT. While no reagents currently exist to deplete cDC post-transplant, the development of such an agent may have significant benefit to transplant patients. Additionally, the promotion of B cell reconstitution may serve to regulate alloresponses following transplantation: our model system clearly demonstrates that as the absence of donor B cells leads to a significant enhancement of donor APC activity, suggesting that B cells act to dampen this activity. Development of these therapeutic strategies may prove useful not just in the bone marrow and haematopoietic stem cell setting, but also in the context of solid organ transplantation, where rejection poses a significant clinical problem.

Cholangiocarcinoma (CCA), or cancer of the bile ducts, is extremely prevalent in people from Laos and Thailand whose staple diet is uncooked fish which harbour the liver fluke, *Opisthorchis viverrini.* There is no stronger link between a parasite and cancer than that between *O. viverrini* and CCA - indeed WHO data suggests that one-third of infected people contract cancer. *In vitro* and *in vivo* studies have indicated that the fluke's excretory/secretory (ES) antigens are mitogenic and likely make significant contributions to the initiation of CCA. To identify these carcinogenic components I undertook two approaches - (1) traditional purification methods to separate ES products, specifically targeting mitogenic proteins, and. (2) bioinformatic screening of 5,000 expressed sequences tags (ESTs) and ES proteins characterized by shotgun proteomic approaches, searching for homologues of molecules that have been associated with human cancers.

The chromatographic protein purification approach utilized a proliferation assay that I developed for measuring cell replication rates in an NIH-3T3 fibroblast cell line. ES products were separated by a combination of ion exchange, hydrophobic interaction, size exclusion and a final ion exchange polishing step. ES products and chromatographically separated ES proteins were added to cultured cells to observe mitogenic activity. A four-step purification process resulted in the isolation of 23 and 31 kDa proteins that stimulated cell proliferation at just picomolar levels. These proteins account for a very small proportion of the total protein biomass (6ppm and 39ppm respectively) secreted by the parasite. Their identities are currently being explored using proteomic approaches with the 31kDa candidate suspected to be OVAE3775, an *Opisthorchis* sequence that has no homology to any known proteins.

Recent information suggested that the mitogen in ES products had affinity for heparin. An alternative purification process was developed using a heparin affinity column to purify ES mitogens as an alternative approach to the classical purification methods detailed above. In combination with ion exchange chromatography a 20kDa candidate was identified with mass spectrometry as a member of the VAL (Venom Allergen-Like) protein family, sharing similarity with secreted proteins from other parasitic helminths including the hookworm activation-associated protein family.

In silico screening of the ESTs and ES peptides revealed by mass spectrometry revealed numerous potentially secreted carcinogens, of which a human growth factor homologue, granulin, was selected for further investigation (*Ov*-Grn-1). This candidate was detected in both the ES proteome and EST datasets. Moreover, the predicted molecular characteristics (alkaline isoelectric points and small molecular weights) corresponded with the purified native mitogens from my earlier work. Recombinant *Ov*-Grn-1 was purified and shows strong mitogenic activity, additionally antibodies against *Ov*-Grn-1 block the ES induced hyperproliferation. Further characterization of the mitogenic molecules from this deadly carcinogenic parasite will shed light on the molecular mechanisms leading to tumour initiation in human Opisthorchiasis, and facilitate the development of new control tools for this debilitating yet neglected pathogen.

Henry Tsao

Treating The Brain In Chronic Low Back Pain

Henry Tsao, May P Galea, Paul W Hodges

Chronic back pain is a major health and economic problem. One intervention that provides some hope is exercise therapy which targets specific impairments in movement and integrates these into activities of daily living. This type of exercise intervention is based on findings that low back pain is associated with deficits in motor control that underlies the way we move. Exercise performed in this manner improves symptoms, reduces disability and reduces pain recurrence. Can exercises therapy alter impairments in movement control? Here we show that motor rehabilitation is associated with improved motor control in people with chronic low back pain. This was dependent on the type and quality of exercise performance. But why is motor control changed in people with low back pain and exercise therapy? To understand the exact mechanisms, we mapped the organisation of the motor region of the brain in people with and without chronic low back pain. The results showed that low back pain was associated with altered organisation of the motor brain, and that these changes were linked to impairments in movement control. However, this is reversible. Specific exercise therapy led to reorganisation of the motor brain towards that observed in healthy individuals, and was linked to meaningful functional outcomes such as improved motor control. These findings are novel and exciting as it highlights the link between changes in the brain and changes in movement control in chronic pain. The results provide unique insight into neural mechanisms that underlie recovery. This work suggests more careful planning of exercises are needed in clinical practice and has helped to fine-tune clinical decision making of treatment strategies for people with chronic low back pain.

Treating The Brain In Chronic Low Back Pain

Chronic low back pain has a major impact on the health and well-being of Australians. It is a major cause of disability and has an economic burden second only to cardiovascular disease. Of the modifiable factors identified, altered motor coordination of the trunk muscles are commonly reported. A failure to recover coordination of the trunk muscles is associated with greater recurrence of pain episodes. Motor rehabilitation that involves training the trunk muscles improves symptoms and function, and reduces recurrence. However, it remained unclear whether deficits in motor coordination can be restored with training, which is the aim of many rehabilitation programs. In addition, the mechanisms that underpin changes in motor coordination remained poorly understood. There is tremendous potential for the motor cortex of the brain to undergo organisational changes following pain and motor training. Thus it was hypothesised that reorganisation of the motor cortex underlies changes in motor coordination, although this had not been investigated.

A series of experiments were undertaken to investigate the organisation of motor cortical inputs to the trunk muscles, the potential for changes with low back pain, and the mechanisms for recovery with motor training intervention. Healthy individuals and individuals with recurrent non-specific low back pain were recruited. Electromyographic activity of the trunk and limb muscles was recorded using a combination of surface and intramuscular fine-wire electrodes. Motor coordination of the trunk muscles was examined through postural and functional tasks. Excitability and topography of motor cortical cells that contribute to activation of the trunk muscles were investigate using transcranial magnetic stimulation.

There were several novel findings. The studies showed for the first time that chronic low back pain was associated with changes in organisation of neuronal networks at the motor cortex. Notably, these cortical changes were closely linked to deficits in motor coordination; that is, the bigger the change in the motor cortex, the greater the deficit in motor coordination of the trunk muscle. But these adaptive changes are reversible. Motor training that involved skilled cognitive activation induced immediate and long term improvements in motor coordination during postural and functional tasks. These improvements were associated with reorganisation of the motor cortex, towards that observed in pain free individuals. Importantly, training-induced changes in motor coordination and brain organisation were dependent on the quality and type of motor training.

The findings provide new insight into the organisation of the trunk muscles at the motor cortex, and unravelled some of the neurophysiological mechanisms that help to explain changes in motor coordination with pain and motor rehabilitation. The results have led to the refinement of management strategies and add weight to the benefits of motor training interventions for chronic low back pain. As low back pain is the most common form of chronic pain in Australia and the most common work-related injury in Western society, improved knowledge and management of this debilitating condition will have a significant impact on the health of many individuals.