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Department of Surgery Austin Health

AUSTIN RESEARCH PRIZE

Surgery & Anaesthesia 2008

AUSTIN RESEARCH PRIZE
SURGERY & ANAESTHESIA
2008

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Table of Contents

The Austin Research Prize in Surgery & Anaesthesia

The Austin Research Prize in Surgery and Anaesthesia was inaugurated in 2003 and supported by Johnson and Johnson Pty Ltd. The main aim of the prize was to foster interest in clinical and basic science research amongst surgical and anaesthesia trainees at all levels and reward excellence in achievement. As the number and quality of submissions increased throughout the years the decision to provide two prizes, one for clinical work and the other for full time academic research was agreed upon in 2007. It is gratifying to note that such interest amongst our trainees is very much alive as evidenced by the large number of high quality presentations submitted this year.

We hope to continue this trend by providing continuing opportunity for our trainees to partake in research programs.

We are grateful to Johnson and Johnson Pty Ltd who have remained strongly committed to supporting research at the Austin. In addition we are also indebted to the senior medical staff of the Austin who have encouraged research amongst the trainees and without whose support much of the work presented here would not be possible.

Prof C Christophi
Head, Department of Surgery
Austin Health

PROGRAM

1700 Refreshments courtesy of Johnson & Johnson Pty Ltd

1800 Introduction

1805 Hou-Kiat Lim – "Safety and Efficacy of Leukocyte Depletion in Cardiac Transplantation"

1815 Mahesha Weerakoon – "Draping and associated equipment for Indwelling catheter manipulation by hospital staff: an assessment of attitudes and adequacy"

1825 Nicholas Campbell – "Laparoscopic camera fogging. Why this occurs and ways to fix it"

1835 Christine Cuthbertson – "The development of macroscopic and microscopic markets of severity during early severe acute pancreatitis"

1845 David Ip – "Point-of-care versus laboratory measurement of prothrombin time and international normalised ratio in patients with liver disease"

1855 Adee-Jonathan Davidson – "Differential cancer/testis antigen expression in colony forming bladder cancer cell populations"

1905 Julian Liew – "An anatomic feasibility study: Nerve transfer to the triceps muscle using the posterior division of the axillary nerve"

1915 Russell Hodgson – "Blockade with soluble ICOS-Ig prolongs survival of cellular xenografts"

1925 Nani Kuswanto – "Non-Invasive cardiac output measurement using pulmonary capnotracking, in comparison with thermodilution technique"

1935 Chew-Lin Yip – "GRP receptors in prostate carcinogenesis"

1945 David Rowe – "Surgical management of Ludwig's angina in Central Australia"

1955 Nieroshan Rajarubendra – " Variations in regulatory T cell infiltration in prostate cancer, BPH and chronic abacterial prostatitis"

2005 Kevin Hung – "The expression of Renin Angiotensin system components in Human Colorectal Liver metastases"

2015 Kaye Bowers – "Comparison of Hospital versus unit based audit data collection"

2025 Adjudication

2040 Announcement of successful trainees & presentation of Prize

Safety and Efficacy of Leukocyte Depletion in Cardiac Transplantation

Lim, Hou-Kiat, Calderone A, Pepe S, Esmore DS, Rosenfeldt FL.

BACKGROUND:
Hearts that are preserved for transplantation undergo ischemic changes that damage the vascular endothelium. Upon reperfusion, white blood cells adhere to damaged endothelium and cause vascular and myocardial damage. Special filters are available that temporarily remove the white blood cells from the blood. The aims of the present study were to compare the efficacy and safety of the different leukocyte filters in a clinical setting and to study the effect of leukocyte filtration on clinical outcomes from cardiac transplantation.

HYPOTHESIS:
In a clinical setting, cardioplegia filters are most effective in reducing leukocytes. The reduction of leukocytes will result in an improved biochemical and clinical response.

METHODS:
In a prospective pilot study, 16 patients were randomized to leukocyte depletion or normal re-infusion and reperfusion. Every aspect of organ procurement and preservation in the two groups were identical with standard practice until re-infusion with blood containing the cardioprotective solution and re-perfusion with blood. Patients allocated to the leukocyte depleted group (LD) utilized a leukocyte depleting (LD) cardioplegia filter for re-infusion and a LD arterial line filter for reperfusion.

RESULTS:
Different classes of leukocyte filters had different efficiency. In this clinical setting, the cardioplegia filter was significantly more efficient than the arterial line filter in the removal of leukocytes from the reaching the transplanted heart. In the interim analysis reported here, the leukocyte filtered group had a trend towards lowered leukocyte counts and improved biochemical trends such as lower serum myocyte injury (Troponin-I,) and significantly lower levels of lipid peroxidation (MDA + 4HNE). Leukocyte filtered group had a higher proportion with better histological outcomes (myocardial rejection). There were no differences in chemokines (TNF-alpha and IL-8) during re-perfusion and post operatively.

CONCLUSIONS:
The results of this pilot study of leukocyte filtration are encouraging, despite the small numbers studied to date. The study will hopefully continue to identify long term benefits in a full clinical trial. This study already demonstrates the safety and feasibility and safety of strategic deployment and efficient use of the leukocyte filter.

Draping and associated equipment for indwelling catheter manipulation by hospital staff: an assessment of attitudes and adequacy.

Weerakoon, M., Lawrentschuk, N.

BACKGROUND:
This study is the first to address the usability and safety aspects of current equipment for indwelling urinary catheter (IDC) manipulation. Our aims were to assess the attitudes of doctors and nurses to infection control, occupational health and environmental waste. Further we assessed the perceived adequacy of available catheter packs, particularly drapes, when performing such manipulations

METHODS:
A self-administered survey instrument was created using an online database to doctors and nurses. The survey covered basic demographic and experience with IDC, attitudes to infection control, occupational health and safety and the environment as well as adequacy of current equipment in containing spillage of urine and/or blood.

RESULTS:
Eighty-seven doctors and 228 nurses completed 315 of 350 (90%) surveys. Doctors and nurses were concerned about infection control, occupational health and safety issues and environmental waste. Incidents regarding spillage of urine and/or blood often go unreported. There were no differences between nurse and doctor, having specialist training in Urology or other experience ($p>0.05$). The second major finding is that available catheter packs, particularly drapes, when performing IDC manipulations are not adequate and spillage is likely occur. These findings were more pronounced in doctors and those with Urology training ($p<0.05$).

CONCLUSIONS:
The attitudes of health professionals involved with IDC manipulations are consistent with other fields, as is the under reporting of episodes of contamination by bodily fluids. The current equipment, particularly drapes, are not adequate at containing urine and blood leading to infection control, occupational health and environmental as well as cost implications.

Laparoscopic camera fogging. Why this occurs and ways fix it.

Campbell N, Lawrentschuk N, Eames, G

BACKGROUND:

Camera lens fogging during laparoscopic procedures hampers vision, increases operating time and has potential associated morbidity. Despite these significant impediments to complication free surgery, the causes and possible solutions for camera fogging have not been well investigated. Current approaches to manage fogging are time consuming and present further, potential associated morbidity. The aims of the study are to:

- Create a model peritoneum that produces reducible results of camera fogging
- Investigate causes of scope fogging
- Compare common methods to reduce fogging

METHODS:

A model peritoneum was made to be as close to the human peritoneum as possible (see diagram below). A normal laparoscopic port, camera, light source and insufflation were used. Various methods to reduce lens fogging (fred, resoclear, chlorhexidine, betadine, normal saline) were compared using a warmed scope (using the scope warmer) and using a scope at room temperature (no scope warmer used). The quality of vision and time for fogging to occur were recorded and repeated 10 times.

RESULTS:

We completed 10 trials of each method. Each method was also subjected to a trial with and without a scope warmer, to evaluate the effect of the warmer in conjunction with the method. Each trial was performed using the model peritoneum in conditions that are known to create fogging. This standard was established as the first component of the trials. Vision in each trial was independently rated by 3 people as 20 (perfect vision), 15 (impaired), 10 (unclear) or 5 (foggy, no effect). Trials indicate that the surfactant fred is significantly better at reducing fogging the lens than other tried methods, irrespective if the scope is warm.

CONCLUSIONS:

A robust model peritoneum that results in reproducible camera fogging was created. The model peritoneum indicates that increased humidity, as created by the heated sausages, results in lens fogging. If the sausages are not hot enough then fogging does not occur. Fred is superior at reducing fogging. Fred was followed by the scope warmer and chlorhexidine. There is little difference as to whether the scope is warm or not.

"The development of macroscopic and microscopic markers of severity during early severe acute pancreatitis"

Dr Christine Cuthbertson, General Surgery SST (Surgeon Scientist stream)

BACKGROUND:

Severe acute pancreatitis is characterised by pancreatic necrosis, resulting in local and systemic inflammation. Predicting the severity of pancreatitis in the early stages is important for treatment planning. Furthermore, understanding the early course of disease helps plan effective treatment.

This study investigates the time course of early pancreatitis pathology in a rat model. It will focus on lung oedema, pancreatic acinar necrosis, necrosis and haemorrhage.

METHODS:

Thirty-nine male Wistar rats weighing approximately 300g were induced with severe pancreatitis by bilio-pancreatic infusion of 3% sodium taurocholate. Animals were killed at 30 minutes, 1, 2, 4, 6 and 24 hours after induction. A further five normal animals were killed for comparison.

At autopsy, macroscopic pancreatitis severity scoring (maximum 15) was performed, based on pancreatic oedema, necrosis, haemorrhage, ascites, and extra-pancreatic fat necrosis. Microscopic severity was assessed using quantitative histological severity of pancreatic acinar necrosis, pancreatic oedema and peri-pancreatic haemorrhage. The right lung was oven-dried to compare wet and dry lung weights to assess pulmonary oedema.

The Mann Whitney test is used for comparison of means, and results are expressed as: Mean (95% confidence interval). Linear regression is used to test trends over time.

RESULTS:

Six hours after induction, pancreatitis is macroscopically advanced, with a severity of 7.9 (6.36, 9.39) compared to zero in normal rats ($p<0.001$). Lung water content is trending downward (76.9%: 74.2, 79.5) in comparison to normal (80.0 (78.5, 81.5); $p=0.06$). However, objective microscopic red cell count and oedema quantification are not different to normal. Microscopic severity score is increased at 6 hours (14.7 (-12.6, 41.9)) compared to normal (1.8 (0.76, 2.84), $p=0.03$.

Macroscopic severity increases significantly over the first six hours (adj. R squared 0.620, $p<0.01$). However, there is no linear correlation between time and lung oedema, microscopic necrosis, microscopic pancreatic oedema or overall microscopic severity.

At 24 hours, the disease has progressed to severe acute pancreatitis. The macroscopic severity increases from 4.7 (3.8-5.6) in with early pancreatitis (6 hours or less) to 10.1 (9.0-11.3) at 24 hours ($p<0.001$). The median necrosis trends upwards from 2.6 to 3.7% ($p=0.06$). Further results at 24 hours are pending.

CONCLUSIONS:

Macroscopic severity increases linearly over the first six hours of experimental acute pancreatitis. Microscopic measures of acute pancreatitis are much more variable and do not increase linearly during early pancreatitis. Microscopic evidence of severity is more reliable at 24 hours, although it remains variable.

Point-of-care versus laboratory measurement of prothrombin time and international normalised ratio in patients with liver disease

D Ip, N Scurrah

BACKGROUND:
Prothrombin Time (PT) and International Normalised Ratio (INR) are markers of synthetic function in patients with liver diseases of varying severity. One of the main limitations of the conventional laboratory derived PT and INR is the time taken from specimen collection to a result being available. This is of critical importance in the setting of invasive or operative procedures where decisions regarding drug or coagulation factor therapy for bleeding diathesis are frequently made empirically whilst waiting for laboratory results. Point-of-care testing if proven to accurately match laboratory derived PT and INR, would allow real-time monitoring and therapy to be guided to potentially reduce the amount of procoagulant administration and blood loss when compared with empirical therapy.

Our hypothesis is that Point-of-care (POC) testing with the Protime Microcoagulation System (International Technidyne Corporation, Edison, NJ, USA) will agree closely with conventional laboratory derived PT and INR, within a clinically relevant range, in patients with coagulopathies secondary to liver disease

METHODS:
Patients with liver disease undergoing routine blood testing had, at the time of blood collection, an additional small sample collected and immediately processed using the Protime Microcoagulation System. Results were then later matched with those derived from conventional laboratory testing and analysed using linear regression and a difference vs mean (Bland-Altman) plot. We define a clinical acceptable limit of agreement (bias +/– 2sd) for PT and INR to be +/– 4 seconds and +/– 0.3 respectively.

RESULTS:
45 samples were taken. The Protime Microcoagulation System returned no result in 16 samples due to either no clot being detected (4) or an error in machine sampling (12). The remaining 29 samples were analysed. The regression coefficient of the POC versus lab derived PT and INR are 0.895 and 0.898 respectively. The difference versus mean plot of PT showed a mean difference [95% CI] of 0.0 seconds [–0.87 to 0.87] whereas the plot of INR showed a mean difference [95% CI] of -0.3 [– 0.38 to – 0.21]. The limits of agreement are –4.5 to 4.5 seconds for PT and –0.75 to 0.15 for INR.

CONCLUSIONS:
A large percentage of samples with no result, in addition to INR testing returning a negative bias and limits of agreement for both INR and PT outside our clinically acceptable range does not allow the use of this POC device to replace traditional laboratory testing to guide clinical decision making in patients with liver disease.

Differential cancer/testis antigen expression in colony forming bladder cancer cell populations

Davidson A-J, Quirk J, Gedye C, Browning J, Bolton DM, Davis ID

BACKGROUND:

1. Only a specific population of bladder cancer cells has the ability to reconstitute tumours and to form colonies in vitro.
2. These cells have a different Cancer/Testis antigen (CTAg) expression profile compared to the overall unsorted cell population.
3. These differences allow immunologic targeting of the cells that are destined to cause relapse and death from cancer.

METHODS:

Commercially available bladder cancer cell line HT1376 was cultured in a colony forming agar assay. Colonies were harvested at 4 weeks. The clonogenic fraction was determined using a previously described method. Complementary DNA was made from the unsorted and colony cell population. Comparative expression of CTAg was determined using quantitative real-time RT-PCR.

RESULTS:

Successful growth of colony cells was achieved using the agar assay. The clonogenic fraction was 1/32. CTAg expression between the two populations was variable (table). Importantly, expression of the MAGE-A4 CTAg was six hundred times more highly expressed in the colony cells than the unsorted cell population, suggesting a functional link between MAGE-A4 expression and colony-forming capacity.

Table 1.Relative expression of CT antigens in colony forming cell population, relative to unsorted cells.

Cancer/Testis Antigen	Relative mRNA expression
NY-ESO-1	0.74
LAGE	0.36
MAGE-A3	0.47
MAGE-A4	602.58
MAGE-A8	1.65
SSX1	0.21

CONCLUSIONS:

These preliminary data indicate that only a small subpopulation of cells in this long-established cell line have the ability to form colonies. Moreover these colony forming cells exhibit a different CTAg profile to the majority cell population. Specifically the CTAg MAGE-A4 is six hundred times more highly expressed. Further work will involve targeting these cells with HLA-restricted anti-MAGE-A4 T lymphocytes to demonstrate that immune-mediated destruction of MAGE-A4-positive cells results in reduced colony-forming potential.

An anatomic feasibibility study: Nerve transfer to the triceps muscle using the posterior division of the axillary nerve.

Liew J H, van Zyl N

BACKGROUND:

This study proposes the co-aptation of the posterior division of the axillary nerve to the lateral head of triceps nerve as a new, alternative option for triceps reconstruction in the tetraplegic patient.

This study provides anatomical data in order to appraise the feasibility of nerve transfer to the triceps using the posterior division of the axillary nerve.

METHODS:

Morphologic features of the axillary nerve from the quadrangular space and the radial nerve from the triangular space were studied in 9 cadaveric arms under 2.0x loupe magnification. Nerve lengths, diameters, and branches were recorded.

RESULTS:

Average arm length was 312 mm. The average diameter of the posterior division of the axillary nerve was 2.5 mm whilst that of the lateral head of triceps nerve was 2.1 mm.

Nerve transfer was possible in all upper limbs except one where no branch to the lateral head of triceps could be identified. In full adduction the average overlap of the nerve transfer was 16.75mm, whereas, when the arm was abducted to 90 degrees, the average amount of nerve overlap was 10.5mm.

CONCLUSIONS:

Nerve transfer from the posterior division of the axillary nerve to the lateral head of triceps is anatomically possible. It provides a possible alternative to reconstruct elbow extension with the advantages of preserving the anatomy and biomechanics of the native muscles, avoiding the need for synthetic prosthesis as well as avoiding donor defects from tendon graft harvest.

Blockade with soluble ICOS-Ig prolongs survival of cellular xenografts

Hodgson R, Christiansen D, Ierino FL, Sandrin MS

BACKGROUND:
Xenografts are one possible solution to the lack of donor organs for diseases such as Diabetes Mellitus. T cell costimulatory pathways are integral to acute cellular rejection against these grafts. Inducible Co-Stimulator (ICOS) pathway blockade has been shown to prolong allograft survival, but there is limited data for xenograft models. Our hypothesis is that local expression of the fusion molecule ICOS-Ig by cells in allograft or xenograft models will prolong survival of cellular grafts.

METHODS:
Porcine Iliac Endothelial cells (PIEC) were transfected with cDNA of the fusion molecule ICOS-Ig. Intracellular and secreted expression was confirmed and quantified using immunoperoxidase staining and Western Blot analysis. In vitro testing of supernatant in mixed lymphocyte reactions was performed. In vivo survival was examined using a subcutaneous graft model in mice.

RESULTS:
ICOS-Ig containing supernatant gave a 99.5% reduction in proliferation of an allograft mixed lymphocyte reaction. Similarly, xenogeneic proliferation was inhibited by 84.3%. In addition an 84.5% reduction in proliferation was observed when PIEC expressing ICOS-Ig were used as stimulators. PIEC-ICOS-Ig xenografts showed prolonged survival compared to wild-type PIEC xenografts (mean survival 34 vs 12 days, p=0.0025) in a subcutaneous graft models in Balb/c mice.

CONCLUSIONS:
Blockade of T cell co-stimulation by the fusion molecule ICOS-Ig has been demonstrated to decrease proliferation in allograft and xenograft in vitro models. Further, there is significant prolongation of survival of PIEC transfected with ICOS-Ig in vivo. These data suggest that further investigations for the role of T cell co-stimulatory blockade in xenografts, through the local expression of ICOS-Ig, are warranted.

Non-Invasive cardiac output measurement using pulmonary capnotracking, in comparison with thermodilution technique

Dr Nani Kuswanto

BACKGROUND:

Cardiac output measurement in anaesthetised patients undergoing a major surgery is desirable. However, the available methods of cardiac output monitoring are invasive, operator dependent or are associated with potentially serious complications and expense.

We have developed an automated non-invasive technique to continuously measure pulmonary blood flow in ventilated patients. This method is called pulmonary capnotracking. A baseline cardiac output measurement is obtained during a change in alveolar ventilation, using the differential Fick principle. Continuous tracking of cardiac output is then done by measuring carbon dioxide elimination by the lungs.

METHODS:

At the Austin Hospital, we did a pilot study examining 18 patients undergoing elective cardiac surgery. Arterial line and Pulmonary Artery catheters were inserted routinely. The method of induction and maintenance of anaesthesia were chosen by the anaesthetist. Once the patient was fully anaesthetised, the device was connected to the breathing circuit. Paired measurements of cardiac output were obtained using bolus thermodilution (average of 3 boluses) and the capnotracking method. Results were logged to computer in real time. Measurements ceased during cardiopulmonary bypass (CPB) and recommenced after weaning from CPB, prior to transfer from the operating table to intensive care unit. Statistical analysis was done using the method of Bland–Altman, and calculation of the correlation coefficient.

RESULTS:

163 measurements were collected from 18 patients. In comparison with thermodilution, the mean bias was -0.19 L/min, standard deviation of difference of 0.90 L/min, giving upper and lower limit of agreements of +1.57 and -1.95 L/min. r = 0.79. The method successfully tracked a cardiac arrest in one patient and reliably followed the fall in cardiac output accompanying run onto CPB.

CONCLUSIONS:

Cardiac output measurement using the capnotracking method delivers agreement with thermodilution technique using the existing equipment available on modern anaesthetic workstations. It has potential for continuous non-invasive measurement of cardiac output on a routine basis in ventilated patients during surgery and in critical care.

GRP receptors in prostate carcinogenesis

Chew – Lin Yip, Liesl Ischia, Joseph Ischia, Oneel Patel, Damien Bolton, Graham Baldwin, Arthur Shulkes,

BACKGROUND:

It has been suggested that neuroendocrine cells have mitogenic effects on adjacent cancer cells contributing to androgen independent growth in hormone refractory prostate cancer1. Gastrin-releasing peptide (GRP) is the prototypical neuroendocrine growth factor. It is a 10 amino acid amidated peptide which is widely distributed in the central nervous system and the gastrointestinal tract. It is produced from a 125 amino acid precursor proGRP. ProGRP also gives rise to several peptides from its C-terminal end.

It was thought that amidated GRP was the only biologically active fragment. However, recently it has been shown that proGRP is biologically active and may in fact be the predominant form in cancer tissues2. While there is preliminary evidence linking proGRP to prostate carcinogenesis, the nature of the receptors mediating any potential actions of proGRP has not been investigated.

METHODS:

Using radiolabelled GRP, proGRP47-68, and proGRP80-97, the receptor status of three prostate cancer cell lines- hormone sensitive (LNcap) and hormone refractory (PC-3, DU-145)- were characterised by competitive binding assays.

RESULTS:

All three cell lines express receptors for GRP but with far greater number on the androgen –independent PC-3 as compared to the androgen dependent LNCaP. Binding sites for proGRP were detected in all three cell lines.

CONCLUSIONS:

Prostate cancer cell lines contain binding sites for both GRP and proGRP. The nature and biological activity of the peptides that bind to these putative receptors require further investigation.

A successful outcome will enhance current knowledge of the role of proGRP and GRP in the development of prostate cancer and provide the basis for future novel treatments such as radiolabelled GRP/proGRP analogues for radiotherapy and cytotoxic chemotherapy.

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[2] Patel O, Dumesny C, Shulkes A, et al. C-terminal fragments of the gastrin-releasing peptide precursor stimulate cell proliferation via a novel receptor. Endocrinology. 2007; 148:1330-9.

[3] Zheng R, Iwase A, Shen R, et al. Neuropeptide-stimulated cell migration in prostate cancer cells is mediated by RhoA kinase signaling and inhibited by neutral endopeptidase. Oncogene. 2006; 25:5942-52.

Surgical Management of Ludwig's Angina in Central Australia

David ROWE, Fred BOSETO, and Jacob JACOB. Department of Surgery, Alice Springs Hospital, Northern Territory, Australia.

BACKGROUND:

Ludwig's angina (LA) is a potentially life threatening condition of the upper areodigestive tract that often involves the co-ordinated and combined efforts of the surgeon, anaesthetic team and intensive care. In Alice Springs, due to the vast distances that typically separate our patients from medical care, patients often present late and with potential if not actual airway compromise. Management of this condition must therefore be definite and with patient care and safety uppermost. Our aim was to investigate the management and incidence of LA at Alice Springs Hospital for the purpose of developing a classification system for risk stratification of patients with LA.

METHODS:

Retrospective chart review from July 2007 to January 1998 examining patients with LA at Alice Springs Hospital over nine and a half years.

RESULTS:

30 patients were identified as having LA of these, 28 (93%) were managed with operative drainage. Twelve were managed in Intensive care (ICU) or High dependency (HDU) post-operatively with only one requiring emergency intubation for airway compromise pre-operatively. Of the 28 who were managed with operative drainage 8 received awake fibreoptic nasopharyngeal intubation, none required tracheostomy. Average length of stay in ICU was 2 days and hospital length of stay was 5 days.

CONCLUSIONS:

The mainstay of our management was operative decompression of the sublingual space, with anaesthetic and intensive care involvement as required. Although our nursing staff copes with a huge variety of surgical conditions, specialized airway observation on the ward is not feasible. In this setting, our management favored early decompression of the sublingual space. We noted that early decompression of the sublingual space was associated with a shorter length of stay compared to other centres where a non-operative approach is favoured.

Variations in regulatory T cell infiltration in Prostate Cancer, BPH and Chronic Abacterial Prostatitis

Rajarubendra N1,2, Elmes M1,2, Bolton DM2, Davis ID1.

BACKGROUND:

Regulatory T cells (Tregs) are a population of T-lymphocytes that can independently regulate adaptive and innate immune responses. They are broadly identified as a small population of CD4+ T-lymphocytes that constitutively express CD25 on their surface and the intracellular transcription factor, forkhead box (FoxP3), amongst other markers. They form an important component of peripheral tolerance and are thus crucial in controlling pathogenic autoreactivity and maintaining immune homeostasis. The immune system may play an important role in the pathogenesis of prostate cancer (PCa) and chronic abacterial prostatitis (CAP). Overactivity of the immune system may be involved in CAP possibly through changes in Treg levels or function. In contrast, local immunosuppression may be important in PCa. We have examined at Tregs proportions in the blood and tissue of patients with benign prostatic hyperplasia (BPH), CAP or PCa.

METHODS:

Fresh tissue from eight patients with BPH, six with CAP and six with PCa were obtained with matching blood. Lymphocytes in the blood were isolated using Ficoll separation and tissue lymphocytes were studied as either single cell suspensions or in tissue frozen sections. Single cell suspensions of the tissue and matching blood lymphocytes were stained for FoxP3 and examined using flow cytometry, whilst frozen sections were stained for CD4, CD8 and FoxP3 using immunohistochemistry (IHC).

RESULTS:

The mean percentages of Tregs in peripheral blood relative to total mononuclear cell number were: 4.12 ± 1.13, 5.96 ± 1.73 and 2.45 ± 1.96 for PCa, BPH and CAP respectively. Tregs were detectable in two of the six CAP tissue while the remaining four had no Tregs in either flow cytometry or IHC samples. Two patterns were evident in the patients with PCa, showing either clear evidence of tumor-infiltrating lymphocytes (TIL) or not. If TIL were present in PCa, the proportion of Treg in the tissue was 2.8 times greater than in the matched peripheral blood sample.

CONCLUSIONS:

Although numbers are small, these results support the hypothesis that CAP may be due to autoimmunity related to low levels of tissue Treg; while high levels of Treg in PCa may lead to local immunosuppression.

The expression of Renin Angiotensin system components in Human Colorectal Liver metastases

Hung, K, C; Muralidharan, V; Angus, P, Christophi.

BACKGROUND:
Colorectal cancer is the second most common internal malignancy across both genders in Australia. Liver metastasis is the leading cause of death in those diagnosed with this disease. Current treatment options include surgical resection, focal ablation, and systemic therapy. However, despite the best of our efforts long-term survival remains poor. This has led to investigations into novel therapeutic means directed against processes of tumourigenesis. Of these, the local renin angiotensin system (RAS) has recently been implicated in important functions of angiogenesis regulation, cellular proliferation, differentiation, migration, formation of extracellular matrix and apoptosis. Furthermore, epidemiological studies have shown reduced incidence of fatal cancers in patients undergoing long-term angiotensin converting enzyme (ACE) inhibitor treatment. We have demonstrated significant tumour inhibitory effects of RAS blockade on a well-established animal model. However, the mechanisms of this effect are currently unknown.

This study aims to characterise the expression of different RAS components in human colorectal liver metastases as compared to tumour bearing liver tissue, correlate this with the findings in the animal model, and relate this to the current understanding of RAS in the role of tumourigenesis.

METHODS:
Snap frozen and fixed tissue from 15 resected colorectal liver metastases were obtained from the Victorian Cancer BioBank, and were used to determine the expression of various RAS components via quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemistry. These methodologies allow quantitative changes in the levels of mRNA transcription, and localization of proteins to be assessed independently. In particular, mRNA of ACE, angiotensinogen, AT1R and AT2R were quantified with qRT-PCR and the presence of ACE, AT1R and AT2R proteins examined with immunohistochemistry.

RESULTS:
ACE mRNA expression was significantly higher in tumour than in the neighbouring liver ($P = 0.000044$). In contrast, Angiotensinogen and AT1R mRNA expression were lower in tumour ($P = 0.000006$ and $P = 0.000047$ respectively). Also, AT2R expression levels were comparable between tumour and liver.

Immunohistochemical staining showed that ACE protein localized to the stromal desmoplasia of the tumour invasion front. In the liver adjacent to tumours, ACE was localised to endothelial cells and around hepatic sinusoids. Similarly, AT1R and AT2R proteins localized to endothelial cells within normal liver and tumour, and to specific cells within stromal tissue.

CONCLUSIONS:
The results demonstrate differential expression of RAS components in tumour versus tumour bearing liver, with results closely mimicking those obtained in our animal model. This adds support to the clinical relevance of our animal model with human disease. The findings also offer possible explanation of the mechanisms underlying anti-tumourigenic effects of RAS blockade, which may be acting via disruption of paracrine interactions between tumour and host RAS components.

Comparison of Hospital versus unit based audit data collection

K. Bowers, C Christophi, V. Muralidharan.

BACKGROUND:

Traditionally within hospitals, information regarding patient admissions, diagnoses, procedures and complications have been collated by Health Information Services. In this age of evidence based medicine it has become increasingly important to record detailed data in order to evaluate patient care and outcomes. Hospital based data is not collated specifically for the purpose of surgical audit. It is often of poor quality and difficult to retrieve and its usefulness as surgical audit tool is thus limited. The Austin Hepatobiliary and Transplant Unit has its own database, with data verified on a weekly basis in a consultant led team meeting.

Aims: To evaluate the quality and retrievability of patient data collated by the hospital Health Information Service as compared to the Hepatobiliary Unit's database.

METHODS:

A written request for the following data for the Hepatobiliary Unit was given to both the unit's data manager and the Health Information Service:

1. The number of admissions with selected diagnoses over a 12 month period
2. The number of selected procedures performed over a 12 month period
3. A list of selected procedure specific complications over a 12 month period
4. Selected procedure specific key performance indicators over a 12 month period
5. A list off all surgical complications for the Hepatobiliary Unit over a 4 year period

The unit's database was considered the gold standard and the hospital database compared to this.

RESULTS:

Records of admission by diagnosis and surgical procedures showed considerable inaccuracies in the hospital database report. A comprehensive record of procedure specific complications was easily extracted from the unit database. Many important procedure specific complications were not retrievable from the hospital database due to the lack of specific coding A list of surgical complications was readily retrievable from the unit database. No such list could be generated by the Heath Information Service as diagnoses are recorded without any indication as to whether they represent a complication or are part of the disease process. No data could be provided by the Health Information Service regarding key performance indicators for specific procedures.

CONCLUSIONS:

There are considerable deficiencies and inaccuracies in patient data collated by health information services. This data is difficult to retrieve and the extraction of useful information often requires significant time spent trawling through cumbersome spreadsheets. Data regarding complications is particularly lacking and accurate data cannot be obtained without review of individual patient histories. Unit specific databases should be kept for the purpose of surgical audit.

Austin Surgery Academic Research Program

Research Higher Degree (RHD) Program

The Department of Surgery strongly encourages the undertaking of RHD by research (PhD, MD M Surg and MSc). The main focus of such research is related to hepato-biliary-pancreatic disorders, organ transplantation and regulatory peptides. Students from both the medical and biomedical fields are welcome. There is also strong international interest from regional centres in this program leading to international post doctoral students undertaking this course.

Currently active research projects include the treatment of liver metastases by vascular disrupting agents, macromolecular drugs and hyperbaric oxygen, the role of liver regeneration in tumour growth, the role of microcirculatory disturbances and hyperbaric oxygen in severe acute pancreatitis, xenotransplantation and the role of regulatory peptides in the development of liver, colon, prostate and kidney tumours. In vivo and in vitro models for each of these projects are well established in the Department. Clinical material and tumour banks are extensively used.

Advanced Medical Sciences Program

The Department of Surgery also conducts an Advanced Medical Science course for medical undergraduates in their third year. The Department is well situated to provide the medical undergraduate with extensive exposure to basic science research in an environment that also provides a close relationship with clinical medicine. This allows medical undergraduates to fulfil their research requirements during the 12 months of their attachment. The research projects offered are the same as those offered to the Honours and RHD candidates.

Undergraduate Research Experience Program

A limited number of positions are available for third year BSc. and B Biomed Sci. students to obtain research experience in basic laboratory science. The Department is in an excellent research environment for science students to take advantage of research work experience in a hospital setting. All three research groups offer this program which is designed to give students an indication of what research is about, and to determine whether they are interested in completing their studies with an Honours year in the Department.

Students will rotate through the different laboratories within the department and gain experience in the techniques used by the various research groups. This will involve one afternoon per week for six weeks during semester 2. Student selection will be based on interview and academic record. A $500 disbursement will be awarded to the selected students.

Applications must be submitted to the department by the 30th of June the preceding year.

Honours Program:

The Department of Surgery at Austin Health has a strong undergraduate research program that encourages scientific research by both medical and biomedical students. These programs are supported by established research projects, enthusiastic and easily accessible supervisory staff, close and friendly supervision, excellent infrastructure and a reputation for progression to research higher degrees supported by research grants. A number of research programs are available to suit the needs of a varied population of potential students.

Research for Clinicians

The philosophy in the Department of Surgery is to encourgae scientific research at all levels in both the clinical, basic science and translational aspects. We also endeavour to establish strong links with other departments to develop collaborative research including the Peter McCallum Institute, and clinical departments such as Anaesthesia, Radiology, Oncology and Intensive Care. The department has also developed detailed surgical databases for both general surgery and specialist HPB disorders. Data collected within these provide a solid base for developing short term clinical studies. All such projects will aim to have the results published in a peer reviewed clinical journal within a year of completing the study.

Research for Junior Hospital Doctors

Recognizing the need for small project based clinical studies for junior hospital medical officers (Interns, HMO 2 and 3) we offer a range of clinical and mixed projects. These are available to anyone interested in developing a future career in surgery. They are structured to be completed within an year to enable a full time junior doctor to complete without enrolling for a formal research degree.

Research for Surgical Trainees

Surgical trainees interested in an academic career will have strong backing from the department to enrol full time in one of the Research Higher Degrees. In addition we also support all surgical registrars, in both accredited and un-accredited positions, to undertake serious research concurrent with their clinical work. These are mostly small project based clinical studies involving data from our clinical databases, hospital medical records and where necessary, tissue from the Victorian Tissue Bank.

Expectations and Outcomes of Research

The departmental philosophy supports the timely completion of all research undertaken by providing the necessary facilities, mentorship, technical expertise and funding support. In general everyone who undertakes research activities in the department will be expected to present their results at local, national or international meetings and be strongly encouraged to publish in peer reviewed journals. All full time enrolled research students are expected to present their work at the annual Austin Research Week and at any other appropriate conference. All clinical research undertaken by surgical trainees and junior hospital doctors will be encouraged to be presented at the annual Austin Surgery Research prize.

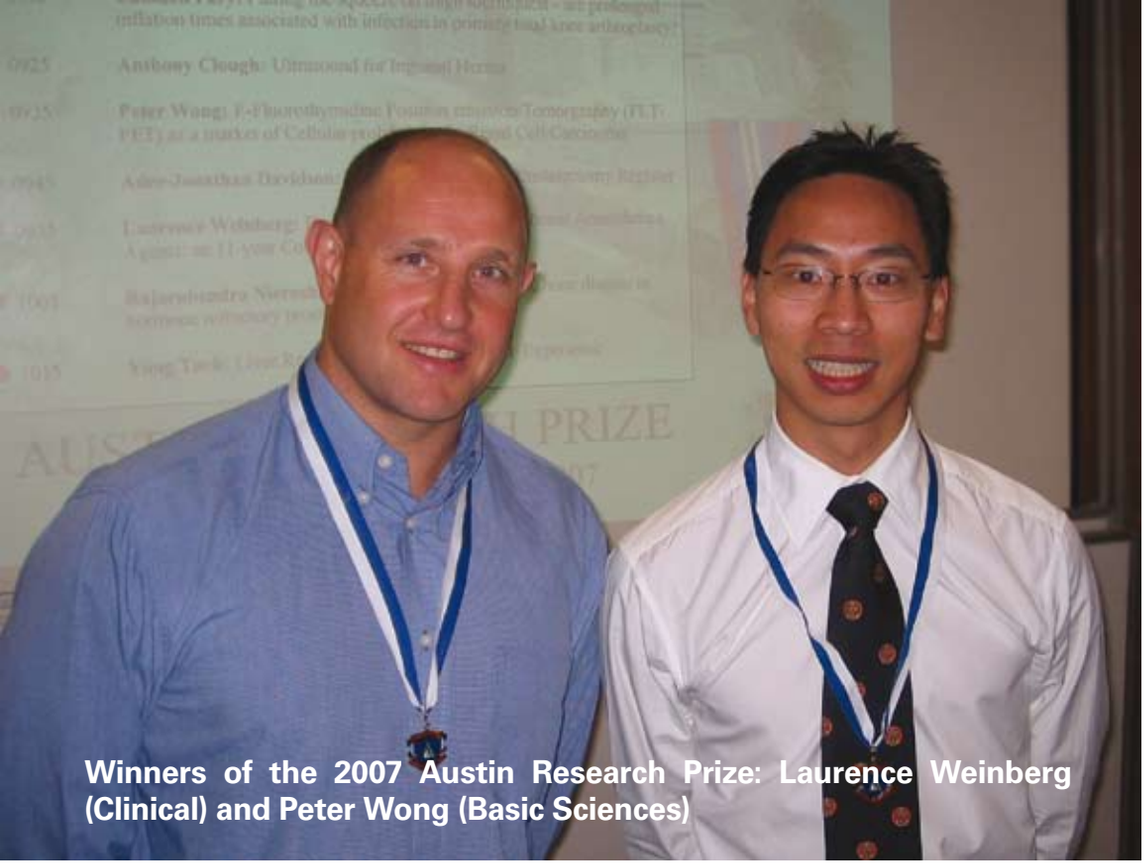
> "The students, supervisors and research staff here are very skilled and have excellent technical abilities. The people here are always willing to lend a helping hand. We really do operate as a closely knit group".
>
> - Jaclyn Neo
> RHD Student

Austin Research Week

This event celebrates the research undertaken at Austin Health and highlights the breadth and excellence of such research. It is an opportunity to learn what others are doing, to facilitate new research collaborations, and to encourage new students and junior researchers to undertake a research career at the Austin.

Austin Research Prize

The Austin Research Prize is open to all Austin Health trainees from Surgery, Anaesthesia, and Intensive Care units. Submissions are sought for presentation in November at the end of the surgical education program. The prize is sponsored by Johnson & Johnson and consists of a medal that is presented to the winner. The names of the winners are etched on the Austin Research Prize plaque.



Winners of the 2007 Austin Research Prize: Laurence Weinberg (Clinical) and Peter Wong (Basic Sciences)

Winner of the inaugural Austin Research Prize 2003: Mehrdad Nikfarjam

AUSTIN RESEARCH PRIZE
PAST WINNERS

2003: **Mehrdad Nikfarjam** - The Influence of Vascular Inflow Occlusion on Progressive Liver Necrosis and Microvasculature Following Interstitial Laser Thermotherapy

2004: **Nathan Lawrentschuk (Joint Winner) -** Tumour Hypoxia in Renal Cell carcinoma using Polarographic Oxygen Sensor Measurements, Immunohistochemistry and serum Osteopontin.

Stephen Warrillow (Joint Winner) - A randomised, double-blind, placebo-controlled cross-over pilot study of glibenclamide in patients with septic shock

2005: **Nathan Lawrentschuk** - In-vivo tumour hypoxia, angiogenesis and characterisation of carbonic anhydrase IX expression with xenografted human Renal Cell Carcinoma in animal models using 124I-cG250 Positron Emission Tomography, Biodistribution, and Oxygen studies.

2006: **Cris Cuthbertson** - Capillary morphology is changed by severe acute pancreatitis and is improved by hyperbaric oxygen.

2007: **Peter Wong (Basic Science Prize)** - 18f-Fluorothymidine Positron Emission Tomography (Flt-Pet) As A Marker Of Cellular Proliferation In Renal Cell Carcinoma

Laurence Weinberg (Clinical Prize) - Pharmacoeconomics Of Inhalational Anaesthetics Agents: An 11-Year Cost Identification Analyses

AUSTIN RESEARCH PRIZE WINNER 2003

Impact of blood flow occlusion on direct and indirect laser induced thermal liver injury

M Nikfarjam, C Malcontenti-Wilson, C Christophi.

BACKGROUND:
Laser, radiofrequency and microwave are common techniques for local destruction of liver tumours by focal hyperthermia. The main limitation of focal hyperthermia treatment is the volume of necrosis that can be achieved. Blood flow occlusion is commonly advocated as an adjunct to focal hyperthermia to increase the volume of tissue necrosis based on macroscopic and histological assessment of immediate or direct thermal injury. This study examines the impact of blood flow occlusion on direct and indirect laser induced thermal liver injury in a murine model using histochemical methods to assess tissue vitality.

METHODS:
Focal hyperthermia produced by laser (Nd-YAG - wavelength 1064 nm) was applied to the liver of inbred male CBA strain mice at 2W for 50 seconds (100J). Treatment was performed with and without temporary portal vein and hepatic artery blood flow occlusion. Animals were killed upon completion of the procedure to assess direct thermal injury and at 24, 48 and 72 hours to assess the progression of tissue damage. The maximum diameter of necrosis was assessed by vital staining for nicotinamide adenine dinucleotide (NADH) diaphorase. Microvascular changes were assessed by laser Doppler flowmetry, Confocal in-vivo microscopy and scanning electron microscopy.

RESULTS:
The direct thermal injury (mean(S.E.) assessed by NADH diaphorase staining was significantly greater following focal hyperthermia treatment without blood flow occlusion than with blood flow occlusion (3.3(0.4)mm vs. 2.9(0.3)mm; P=0.005). Tissue disruption, cracking and vacuolization was more pronounced adjacent to the fibre insertion site in the group treated with focal hyperthermia combined with blood flow occlusion. There was an equivalent increase in the extent of injury following therapy in both groups that reached a peak at 48 hours. The maximum diameter of necrosis in the focal hyperthermia alone group at 48 hours was significantly greater than the focal hyperthermia combined with blood flow occlusion group (5.8(0.4)mm vs.5.3(0.3)mm; P=0.011). The patterns of microvascular injury were similar in both groups, varying in extent.

CONCLUSIONS:
Temporary blood flow inflow occlusion appears to decrease the extent of initial injury measured by vital staining techniques and does not alter the time sequence of progressive tissue injury following focal hyperthermia therapy.

AUSTIN RESEARCH PRIZE WINNER 2004 (JOINT)

Tumour Hypoxia in Renal Cell carcinoma using Polarographic Oxygen Sensor Measurements, Immunohistochemistry and serum Osteopontin.

N Lawrentschuk, C Murone, AMT Poon, J Sachinidis, G O'Keefe, LG Johns-Putra, Z. LIU, I Davis, AM Scott, DM Bolton

BACKGROUND:

The purpose of our research is to evaluate oxygen levels and angiogenesis within renal cell cancers (RCC), as evidence suggests they are hypoxic, given their resistance to radiotherapy and chemotherapy. Hypoxia has now been shown in other tumours to correlate with resistance to treatment and poor prognosis. Our study builds on the finding of hypoxia in RCC and explores its relationship with immunohistochemical markers of hypoxia and a new novel marker of hypoxia in tumours, serum osteopontin

METHODS:

Patients who were undergoing radical nephrectomy for RCC had : 1) Evaluation of oxygen levels (pO2) within their renal cell cancers in vivo using a Polarographic Oxygen Sensor. 2) Immunohistochemistry including microvessel density to confirm at a sub-cellular level the relationship of hypoxia with the expression of proteins associated with hypoxia and angiogenesis in RCC and 3) Human osteopontin ELISA immunoassay techniques to analyse the serum levels of osteopontin.

RESULTS:

30 patients have been recruited thus far and we have demonstrated that RCC are relatively hypoxic (median pO2 7.2mmHg) compared to normal renal tissue (26.3mmHg). Microvessel density is increased in RCC compared to normal tissue indicating increased angiogenesis. Other markers if hypoxia were also increased. Serum osteopontin in patients with RCC was greater at 17.65 $\pm$ 5.3 ng/ml (mean $\pm$ 95% C.I.; range 5-41) compared to controls 8.75 $\pm$ 2.17 ng/ml (range 8-12).

CONCLUSIONS:

Renal cell cancers are relatively hypoxic and more angiogenic compared to normal tissue within the same kidney. This may explain resistance to radiotherapy and chemotherapy whilst helping to identify future therapeutic targets in the management of advanced renal cell cancer. Serum osteopontin has been demonstrated to be raised in RCC and is a novel tumour marker for renal cell carcinoma.

AUSTIN RESEARCH PRIZE WINNER 2004 (JOINT)

A randomised, double-blind, placebo-controlled cross-over pilot study of glibenclamide in patients with septic shock

Stephen Warrillow, Moritoki Egi, Rinaldo Bellomo

BACKGROUND:

Severe sepsis often causes a hypotensive shock state. Hyperpolarisation of the vascular smooth muscle cell membrane, due to the marked K+ efflux prevents Ca2+ entry into cells and may be responsible for 'vasoplegia'. Glibenclamide (normally an oral hypoglycaemic agent) blocks the ATP-dependent K+ channel and may prevent hyperpolarization this restoring intra-cellular Ca2+ levels and re-sensitising vascular smooth muscle to noradrenaline. Animal studies have demonstrated that glibenclamide restores vascular sensitivity to noradrenaline. However, this effect has not been previously studied in humans.

Objective: To test whether glibenclamide restores noradrenaline responsiveness in septic shock patients.

METHODS:

Prospective, double-blind, placebo-controlled cross-over pilot study, in 10 patients with septic shock requiring an infusion of noradrenaline to receive either enteral glibenclamide 20mg or placebo. After twenty-four hours, each patient crossed over to receive the alternative therapy. The primary end-point was the change in noradrenaline infusion rate over time with maintenance of target mean arterial pressure. Secondary end-points included changes in heart rate and serum lactate levels.

RESULTS:

Glibenclamide was adequately absorbed enterally and, as expected, induced a significant decrease in serum glucose concentration (Mean glucose: 5.97 $\pm$ 2.17 vs 7.65 $\pm$2.43 ($P<0.0001$) and increased the need for parenteral glucose administration. During glibenclamide treatment mean noradrenaline requirements fell from 13 to 4 µmol/min compared to a change from 19 to 7 µmol/L for placebo. The two changes represented a decrease of 78.9% and 71.1% in dose respectively (NS). There were also no significant changes in heart rate, mean arterial blood pressure and lactate concentration.

CONCLUSIONS:

Glibenclamide was well absorbed enterally and exerted its hypoglycaemic effect reliably. However, it failed to achieve a greater reduction in noradrenaline dose than placebo. Our observations suggest that, in septic humans, blockade of ATP-potassium dependent channels does not have a potent effect on vasomotor tone.

AUSTIN RESEARCH PRIZE WINNER 2005

In-vivo tumour hypoxia, angiogenesis and characterisation of carbonic anhydrase IX expression with xenografted human Renal Cell Carcinoma in animal models using 124I-cG250 Positron Emission Tomography, Biodistribution, and Oxygen studies.

Nathan Lawrentschuk, C Murone, A Rigopolous, A Mountain, D Wang, G O'Keefe, G Jones, FT Lee, Ian Davis, Andrew M Scott, Damien M Bolton

BACKGROUND:

Hypoxia stimulates angiogenesis and has been demonstrated in tumours where it correlates with resistance to treatment and poor prognosis. We have demonstrated hypoxia in human Renal Cell Carcinoma (RCC). The purpose of animal models was to further evaluate oxygen levels within RCC whilst also focusing on expression of the protein carbonic anhydrase IX (CA IX). This protein is stimulated by hypoxia and involved in angiogenesis and may be a potential tumour target for imaging and future therapies. The human antibody cG250 binds to CAIX in vivo allowing biodistribution and PET studies when radiolabeled with iodine-124 (I124).

METHODS:

Balb/c nude mice had human RCC (SK-RC-52) xenografted subcutaneously. Tumours were grown to different volumes with oxygen levels measured. Further groups then had the radiolabelled monoclonal antibody 124I-cG250 (that binds to CA IX) injected intravenously and had Positron Emission Tomography (PET), gamma counting and oxygen studies performed on days 0, 1, 2, 3, 5, 7, 10 and 14 post injection. Immunohistochemistry and autoradiography was also performed.

RESULTS:

An inverse relationship between tumour volume and hypoxia within the model was established ($P<0.001$). Furthermore, CA IX was expressed by tumours with maximal uptake of 124I-cG250 on days 2/3 by distribution with gamma counting that could be correlated with uptake on PET imaging. Also, 124I-cG250 as read by gamma counter correlated with noninvasive PET scanning standardised uptake values of the radioisotope within tumours.

CONCLUSIONS:

The xenograft model confirms our previous findings that human RCC are relatively hypoxic compared to normal tissue. Also, that the level of hypoxia is inversely proportional to tumour size. CAIX was confirmed as an imaging and potential therapeutic target in RCC. Finally, a correlation was made between PET scanning with 124I-cG250 and biodistribution within tumours by gamma counting confirming the potential to serially PET scan animals rather than sacrifice in future biodistribution studies. This has major implications for animal ethics and the design of future biodistribution studies that are routinely used to characterised new radioisotopes and radiolabeled antibodies used to treat a variety of cancers.

AUSTIN RESEARCH PRIZE WINNER 2006

Capillary morphology is changed by severe acute pancreatitis and is improved by hyperbaric oxygen.

C. Cuthbertson, K. Su, C. Malcontenti-Wilson, V. Muralidharan, C. Christophi

BACKGROUND:
Severe acute pancreatitis is characterized by alterations to the microcirculation, particularly affecting the capillary tree, which lead to pancreatic necrosis. The morphology of the pancreatic microvasculature is known to be affected in severe pancreatitis, but the effect of hyperbaric oxygen is unknown. The aims of this study are to determine the progression of pancreatic microvascular changes caused by acute pancreatitis and to determine the effect of the administration of hyperbaric oxygen (HBO).

METHODS:
Sixty seven male Wistar rats weighing 250-350g were induced with severe pancreatitis by bilio-pancreatic infusion of 4% sodium taurocholate. Animals were randomised to either HBO treatment or control. HBO treatment (100% oxygen for 90 minutes at 2.5 Atmospheres) was commenced 6 hours following induction of pancreatitis, and continued 12-hourly. Surviving animals underwent microvascular polymer casting of the pancreas at six, 24, 48 and 72 hours following commencement of treatment, and equivalent time points for control animals. Normal and Sham-operated animals also underwent casting. Microvascular casts were created by the injection of freshly prepared Mercox resin through a cannula in the thoracic aorta. The pancreas was removed after 24 hours of polymerisation and further prepared for scanning electron microscopy of the resin cast. Scanning electron micrographs of the casts were compared for capillary density, poor capillary filling, vessel diameter, and major morphological changes.

RESULTS:
Normal pancreatic microvascular casts showed a dense network of capillaries, with multiple anastomoses (Image 1). Significant morphological changes appeared at 24 hours post induction (Image 2). Microvascular casts demonstrated poor capillary filling, decreased capillary density and increased capillary cast diameter. Capillary diameter was increased (from 6.7m to 10.3μm at 24hr, $p<0.01$, and 11.8μm at 48hr, $p<0.001$), capillary heterogeneity was increased (range increased from 13.8μm to 21.4 μm, $p<0.001$) and capillary density was reduced (from 1140μm-2 to 758μm-2, $p<0.01$). These changes occurred at 24hours post induction and were maintained at 48 and 72 hours. Treatment with HBO reduced the severity of microvascular morphological changes at each time point (Image 3). These changes became apparent at 48 hours post induction, and were maintained at 72 hours. At 48 hours, capillary diameter was decreased toward normal (from 11.8μm to 8.4μm, $p<0.01$), range was reduced, and capillary density was increased (from 722μm-2 to 901μm-2, $p<0.01$).

CONCLUSIONS:
Microvascular parameters are affected by acute pancreatitis, with changes detected at 24 hours and maintained until at least 72 hours. HBO improves the microvascular morphology parameters in acute pancreatitis towards normal values. HBO has potential as a unique alternative therapy in acute pancreatitis.

AUSTIN RESEARCH PRIZE WINNER 2007 (Basic Science)

18f-Fluorothymidine Positron Emission Tomography (Flt-Pet) As A Marker Of Cellular Proliferation In Renal Cell Carcinoma

Wong P[1,2]; Lee ST[2,3,4]; Eng J[3;] Murone C[2]; Berlangieri SU[3]; Pathmaraj K[3]; O'Keefe GJ[3]; Byrne AJ[3]; Lawrentschuk N[1,2;] Davis ID[2]; Bolton DM[1]; Scott AM[2,3,4.]

1 Department of Surgery (Urology), University of Melbourne, Austin Health, Heidelberg, Australia. 2 Ludwig Institute for Cancer Research, Austin Health, Heidelberg, Australia. 3 Centre for PET, Austin Health, Heidelberg, Australia. 4 Department of Medicine, University of Melbourne, Austin Health, Heidelberg, Australia.

BACKGROUND:

18F-FLT-PET (Fluorothymidine Positron Emission Tomography) has been used to non invasively measure cellular proliferation in a number of tumour types. However, its role in renal cell carcinoma (RCC) has not been established. We aim to assess FLT-PET in RCC, and to compare it to immunohistological measurements of proliferation.

METHODS:

Patients with suspected RCC suitable for nephrectomy had preoperative FLT and FDG (fluorodeoxyglucose) PET/CT scans. Surgical samples were obtained for immunohistochemical analysis (Ki-67). Qualitative visual grading relative to normal kidney and analysis of maximum standardized uptake value (SUVmax) of each PET scan was assessed using co-registered low-dose 5mm CT and prior triple phase CT imaging. Uptake in RCC using FLT PET was compared to FDG PET. Statistical analysis comparing Ki-67 and SUVmax was performed.

RESULTS:

A total of 19 patients (13 clear cell, 5 papillary and 1 transitional cell carcinoma) underwent preoperative PET scans, with immunohistochemical data available for 13. Visual grading found most tumours had radiotracer uptake that was equal or less than the contralateral kidney. FLT uptake was generally less than FDG. Bivariate analysis showed a positive correlation between Ki-67 & FLT SUVmax (p-value 0.001, r = 0.8) and between Ki-67 & FDG SUVmax (p-value 0.005, r = 0.73).

CONCLUSIONS:

Uptake of FLT in RCC is less than FDG. There is positive correlation between FLT uptake and Ki-67 proliferative index in RCC suggesting that the degree of proliferation within RCC can be predicted by PET imaging. Further study is required to determine whether this correlates with patient outcome.

AUSTIN RESEARCH PRIZE WINNER 2007 (Clinical)

Pharmacoeconomics Of Inhalational Anaesthetics Agents: An 11-Year Cost Identification Analyses

Laurence Weinberg, David Story, Larry McNicol

BACKGROUND:

Anaesthetic departments account for 2-3% of the total hospital budget, with anaesthetic drugs accounting for 5-8% of total pharmacy expenditure. Inhalational agents account for 20% of anaesthetic drugs therefore are one of the areas that are most amenable to immediate cost reduction in the anaesthetic department budget. This study is a cost identification analyses assessing inhalational anaesthetic agent expenditure at Austin Health over an 11-year period. Pharmacoeconomic modeling is used to evaluate strategies to curtail costs.

METHODS:

The number of bottles utilised of three volatile agents (Isoflurane, Sevoflurane, Desflurane) was collected each month for the financial years ending 1997 to 2007. The acquisition costs and the cumulative drug expenditure in dollars for each agent were calculated. Inhalational agent utilisation patterns and unit price changes were evaluated. Pharmacoeconomic modeling using low fresh gas flow anaesthesia was performed to evaluate practical methods for reducing anaesthesia costs. The rational use of the cheaper generic volatile agent Isoflurane was used in pharmacoeconomic cost-containment strategy models.

RESULTS:

For the financial years ending 1997 to 2007, pharmacy acquisition costs for a bottle of Isoflurane (250mL), Sevoflurane (250mL) and Desflurane (240mL) were $157, $336, $170 respectively, and for the financial years ending 2005 to 2007, cost per bottle was $109, $265, $180 respectively. The number of bottles of Isoflurane decreased from 384 bottles/year in 1997 to 204 bottles/year in 2007. The number of bottles of Sevoflurane increased from 226 bottles/year in 1998 to 875 bottles/year in 2007. Desflurane use commenced at Austin Health in 2002 with 34 bottles being used. This increased to 163 bottles/year in 2007. Expenditure for Isoflurane decreased from $88,985/year in 1997 to $22,006/year in 2007. In contrast, Sevoflurane expenditure increased from $11,442/year in 1997 to $274,692/year in 2007. Desflurane expenditure increased from $5,855/year in 2002 to $29,340/year in 2007. Total cumulative expenditure for inhalational agents was $100,427/year in 1997, increasing to $326,038/year in 2007. Pharmacoeconomic modelling demonstrates that the cost of an inhalational agent for a 60-minute anaesthetic, at 1 Minimum Alveolar Concentration, at fresh gas flows of 1L/min (low flow), is $1.54 for isoflurane and $6.89 for Sevoflurane. At fresh gas flows of 6 L/min (high flow), costs increase to $9.20 for Isoflurane and $47.47 for Sevoflurane. Cost modelling reveals if Sevoflurane usage between 1997 and 2007 would have been reduced by 40% per year and substituted for the cheaper inhalational agent Isoflurane, a total savings of $866,565 would have been achieved for this 11-year period. Similarly, conservative cost analyses predicts that if the current trends in volatile anaesthetic agents continue at Austin Health over the next 10 years, if a 40% reduction per year in Sevoflurane usage could be achieved by utilising Isoflurane in its place, a total net savings in excess of $1.8 million will result.

CONCLUSIONS:

Cost analyses of anaesthetic drugs is necessary is today's economic climate. Low flow anaesthesia is a simple but highly effective method of cost minimization for inhalational anaesthetic agents. Cost containment is also influenced by the rational use of available inhalational agents.

Location and Access

The Department of Surgery is located in the Lance Townsend Building (1) within Austin Health, Heidelberg, next to the Austin and Mercy Tower Complexes. Entry is from Burgundy Street (level 3) or from Studley Road (level 1) which is just across the road from Heidelberg railway station. It is just 20 minutes by car or 30 minutes by train / tram from The University of Melbourne, Parkville campus.

A large underground car park with four levels services both hospitals and the university precinct. Entry can be gained from Studley Road (level B3) or Burgundy Street (level B2).

1. Lance Townsend Building
2. Harold Stokes Building
3. Austin Tower
4. Mercy Hospital
5. Main Hospital Entrance
6. Studley Road Car Park Entrance (Level B3)
7. Burgundy Street Car Park Entrance (Level B2)
8. Pedestrian Bridge
9. Studley Road
10. Bell Street
11. Heidelberg Railway Station
12. Burgundy Street
13. Kronheimer Building

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Designed, Produced and Edited by
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2008