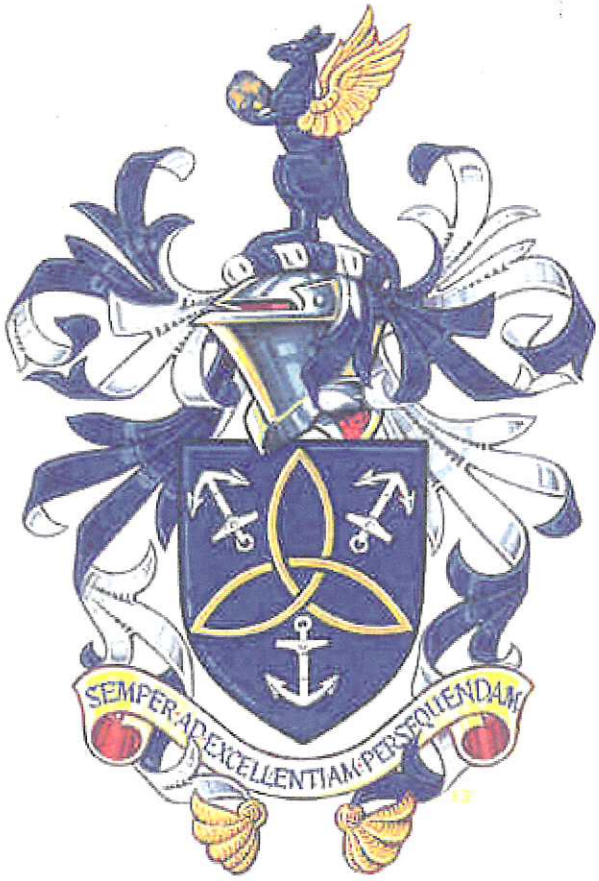

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The Garnett Passe and Rodney Williams Memorial Foundation Frontiers in Otorhinolaryngology 2004 Programme

WEDNESDAY, 28 JULY 2004

5.30 – 6.30pm	Registration	The River Lounge
6.30 – 9.00pm	Welcome Reception	Noosa Ballroom

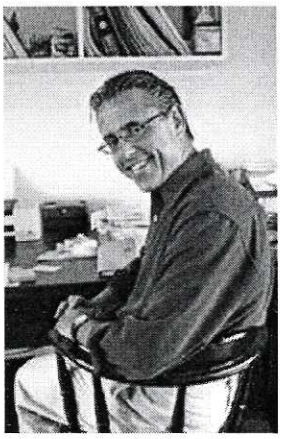
THURSDAY, 29 JULY 2004

8.30am	Opening Remarks	Dr Dean Beaumont
	OPENING ADDRESS	**Chair: Dr Dean Beaumont**
8.30 – 9.10am	The unfolding world of DNA technology	Professor Ross Coppel
SESSION 1	**OTOLOGY**	**Chair: Dr Peter Freeman**
9.10 – 9.50am	Gene transfer and the cochlea	Associate Professor Yehoash Raphael
9.50 – 10.10am	Genetic unravelling of sensorineural deafness	Dr Michel Guipponi
10.10 – 10.30am	Polymers, Neurotrophins, and Cochlear Implants: High Fidelity Sound	Professor Graeme Clark
10.30 – 11.00am	Morning Tea	
SESSION 2	**HEAD AND NECK CANCER**	**Chair: Professor Doug Tracy**
11.00 – 11.40am	Molecular biology in head and neck cancer – How well are we translating?	Dr Joseph Califano
11.40 – 12.00pm	Immunological parameters in NPC	Professor Denis Moss
12.00 – 12.20pm	Growth factors and their implications in head and neck cancer	Associate Professor Andrew Scott
12.20 – 12.40pm	Can gene technology improve the management of head and neck cancer?	Professor William Coman
12.40 – 2.00pm	Lunch	
SESSION 3	**RHINOLOGY**	**Chair: Dr Kevin Kane**
2.00 – 2.40pm	High-density microarray analysis in cancer and allergy – What can be deciphered from transcriptional profiles?	Professor Carl Borrebaeck
2.40 – 3.00pm	Epithelial mucins: Roles in mucosal homeostasis and disease	Associate Professor Mike McGuckin
3.00 – 3.20pm	Genetic determinants in nasal and sinus disease	Dr William Smith
3.20 – 3.40pm	Immune responses in fungal sinus disease and their implications for treatment	Professor Peter-John Wormald
3.40 – 4.10pm	Afternoon Tea	
SESSION 4	**PRESENTATION AND DISCUSSION**	**Chair: Professor John Funder**
4.10 – 4.20pm	Research Australia	Dr Christine Bennett
4.20 – 5.00pm	Open Discussion	

FRIDAY, 30 JULY 2004

	OPENING ADDRESS	**Chair: Dr Dean Beaumont**
8.30 – 9.10am	Reshaping life with stem cells	Professor Ross Coppel
SESSION 5	**HEAD AND NECK CANCER**	**Chair: Professor Doug Tracy**
9.10 – 9.50am	New discoveries in the progression of head and neck cancer	Dr Joseph Califano
9.50 – 10.10am	Evolution of the anatomy and function of the larynx	Professor William Coman
10.10 – 10.30am	Muscle stem cells and gene expression: Some surprises from the laryngeal muscles	Dr Ann Trezise
10.30 – 11.00am	Morning Tea	
SESSION 6	**OTOLOGY**	**Chair: Dr Dean Beaumont**
11.00 – 11.40am	Sensory cell death and regeneration in the cochlea	Associate Professor Yehoash Raphael
11.40 – 12.00pm	Cell and drug-based therapies in the deafened cochlea: New strategies for cochlear implantation	Associate Professor Robert Shepherd
12.00 – 12.20pm	Cell-based therapies for hearing loss	Dr Michelle de Silva
12.20 – 12.40pm	Electrophysiological assessment of vestibular function	Associate Professor James Colebatch
12.40 – 2.00pm	Lunch	
SESSION 7	**RHINOLOGY**	**Chair: Dr Kevin Kane**
2.00 – 2.40pm	Designing therapeutic antibodies	Professor Carl Borrebaeck
2.40 – 3.00pm	Olfactory neural stem cells: A fast moving story	Professor Anne Cunningham
3.00 – 3.20pm	Multipotent stem cells from adult human nose	Professor Alan Mackay-Sim
3.20 – 3.50pm	Advances in imaging in Otolaryngology	Dr Andy Whyte
3.50 – 4.20pm	Afternoon Tea	
SESSION 8	**DISCUSSION**	**Chair: Professor John Funder**
4.20 – 5.00pm	Open Discussion	
5.00pm	Closing Remarks	Dr Dean Beaumont
7.30pm	Conference Dinner	Noosa Ballroom Guest speaker: Dr Norman Swan

DR NORMAN SWAN



Best known for his wide broadcasting experience including the award-winning *Health Report* for ABC Radio National, Dr Norman Swan also hosted *Life Matters* for Radio National and more recently *Health Dimensions* on ABC Television. The high profile show *The Health Report* is a weekly programme dealing with topical medical and health issues for a general audience. The programme won Gold Medals at two New York International Radio Festivals. *Health Dimensions* also focuses on consumer health, while *Life Matters* covers social issues, relationships and education. A Producer with the ABC's Science Unit since 1982, Norman was awarded a Gold Citation in the United Nations Media Peace Prizes for his radio work and has been Australian Radio Producer of the Year.

In 1988 Norman won the Australian Writers' Guild Award for best documentary for his program on Dr William McBride and scientific fraud. He also won three Walkley National Awards for Australian Journalism including the Gold, the most recent in 1997. In 1989 he was awarded Australia's top prize for Science Journalism, the Michael Daley Award.

Prior to presenting *Health Dimensions*, Norman was a guest reporter on *Quantum*, *Four Corners* and *Catalyst*. He created, wrote and narrated *Invisible Enemies* a four part series on disease and civilisation, broadcast on SBS Television, Channel 4 (UK) and in 27 countries. He also co-wrote and narrated *The Opposite Sex* for ABC TV.

In addition to his broadcasting work, Norman also edits his own newsletter, *The Health Reader*, which is published in association with *Choice* magazine. He has also consulted to the World Health Organisation.

The Garnett Passe and Rodney Williams Memorial Foundation

Frontiers in Otorhinolaryngology 2004

Abstracts of Invited Speaker Presentations

THE UNFOLDING WORLD OF DNA TECHNOLOGY

Ross Coppel
Department of Microbiology
Monash University
Victoria

The last ten years has seen the development and application of a number of advanced technologies that probe gene structure and function at the level of the whole organism. Thus we are now able to determine the sequence of all DNA within organisms as diverse as man, mice, livestock, flies, worms, plants including food crops and bacteria and viruses. For every organism so far sequenced, we simply do not yet know what 40%-60% of the genes are doing. Finding the genes within an organism's genomes and deciphering their function and interactions with other proteins will be the work of the next century. Techniques that examine gene expression, protein repertoire, protein interactions and structure for all genes within an organism have been developed and are now generating enormous amounts of data. This talk will review developments in genomics and functional genomics and explain how the data is integrated and mined to provide information about the living cell and how organisms function.

Biography

Ross Coppel is Professor of Microbiology within the Medicine, Nursing and Health Sciences Faculty at Monash University. His laboratory is involved in research into malaria, tuberculosis, autoimmunity and bioinformatics.

Ross is a Howard Hughes Medical Institute International Fellow and an internationally recognised scientist in the fields of the molecular biology of malaria and primary biliary cirrhosis. In 2002 a Third Edition of the book, Reshaping Life, a Guide to Genetic Engineering for the Layperson, Nossal, G.J.V. and Coppel, R.L. was produced. He is a member of an advisory committee that oversees Bioinformatics of the malaria genome project and administers the malaria sequence database for the World Health Organisation. Funding to support his research activities comes from national and international agencies including the National Health & Medical Research Council, the Australian Research Council, the Wellcome Trust, the National Institutes of Health, the United States Agency for International Development, the World Health Organisation and the Bill and Melinda Gates Foundation. In 2003 Ross co-founded Glykoz to commercialise new antibiotics that he and his collaborators have discovered.

GENE TRANSFER AND THE COCHLEA

Yehoash Raphael
Kresge Hearing Research Institute
University of Michigan
USA

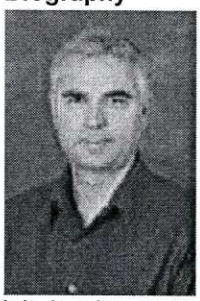
Gene therapy can be of used to protect, repair and regenerate cells in the inner ear. The general concept of gene therapy involves manipulating gene expression by introducing genetic material into cells. At present, the most efficient gene-delivery vectors are recombinant viruses that are engineered to shuttle a transgene into target cells, express the gene, and produce little or no side effects. While viral vectors are not perfect, their quality and safety have been constantly improving. Their utility in inner ear gene therapy has been demonstrated for several specific application.

Hair cells in the organ of Corti are highly differentiated post-mitotic cells and are normally not replaced once lost. This accounts for the irreversibility of sensorineural hearing loss, which is most commonly a result of hair cell degeneration. Protection of the original set of hair cells against degeneration is therefore an important clinical goal. Genes encoding several protective proteins have been shown to enhance hair cell protection following delivery with viral vectors. Among these genes are growth factors and anti-oxidants. The feasibility of gene therapy for applications in the vestibular system has also been demonstrated.

In the complete absence of hair cells, the only current way to restore hearing is via a cochlear implant. While cochlear implants improve the quality of life for many recipients, the success of the procedure is inconsistent and incomplete. A biological enhancement of the cochlear implant may be beneficial. Among the potential applications for the combined gene transfer and cochlear implant procedure are influencing the number and health of surviving spiral ganglion neurons and controlling connective tissue growth in the cochlear fluid spaces. We combined electrical stimulation with neurotrophic factor secretion via gene transfer and enhanced the survival of the spiral ganglion. In addition, viral mediated transgenic expression of BMP and TGF-β1 induced connective tissue growth in the fluid spaces of the inner ear, presenting a model for studying regulation of connective tissue response in the cochlea. Other experiments demonstrated the feasibility of attaching genetically engineered cells onto the implant electrode and delivering protective agents secreted by these cells.

Supported by the Royal National Institute for Deaf People (RNID), GenVec, NIH/NIDCD Grants R01 DC 01634 and R01-DC05401, and P30 grant DC 05188.

Biography



Yehoash (pronounced Yoash) is an inner ear biologist with educational background in audiology and basic biology. He has been on the Faculty of the Kresge Hearing Research Institute at the University of Michigan since 1990 and is currently the Director of the Otopathology Laboratory. In recent years, Yoash's research has been focused on developing gene therapy for protection repair and regeneration in the inner ear. The work involves both the auditory and the vestibular portions of the ear. The work has shown that introducing foreign genes into the inner ear can help protect hair cells and spiral ganglion neurons against degeneration. Recent work using adenovirus-mediated gene therapy has pioneered the ability to grow new hair cells in the living mammalian cochlea. The lab is also engaged in analyzing the structure of the inner ear of mutant mice with auditory or vestibular deficits. Future goals of the projects in the Otopathology Laboratory are to (a) design gene therapy technology for treating hereditary inner ear disease, (b) enhance the ability to generate new cochlear hair cells to accomplish recovery of structure and function of the pathological inner ear and (c) improve cochlear implant function by increasing the biocompatibility of the prosthesis.

GENETIC UNRAVELLING OF SENSORINEURAL DEAFNESS

Michel Guipponi
Genetics and Bioinformatics Division
Walter Eliza Hall Institute of Medical Research
Victoria

Genetic approaches have been exceptionally useful for identifying key components of the auditory system, especially as the inner ear located inside the temporal bone is difficult to access and the amount tissues made of highly specialized cell types are available for analysis. Over the last decade, the hearing research has benefited tremendously from the progress of the human and mouse genome projects. Many important proteins have been identified through positional cloning of genes responsible for monogenic deafness or through the analysis of genetic mouse models. These genes underlying monogenic inherited hearing loss may also play a role in age related hearing loss, the most common cause of hearing impairment. However, only half of the ~100 genes for non-syndromic deafness have been identified indicating that there are still crucial genes and pathways that remain to be investigated.

Besides positional cloning of genes that underlie hearing disorders in human and mice, new tools have been developed to characterize, at molecular level, the inner ear function. These new approaches mainly aim at identifying candidates genes through proteomic (protein-interaction screens), genomic (cDNA libraries, SAGE, DNA arrays) and bioinformatic (sequence analysis, database mining) approaches or combination of these methodologies.

Recently, using positional cloning we have shown that a novel serine protease, TMPRSS3, was mutated in familial and sporadic cases of hearing loss. Genes known to be mutated in deafness can be grouped into functional classes. TMPRSS3, which belongs to the type II transmembrane serine protease (TTSP) family, does not fit in any of the existing group and could represent the first member of a new functional category. We have then started to investigate the role of this family of protease in hearing loss. We used bioinformatic tools to look for all similar protease in the human and mouse genomic sequences. We have determined their inner ear expression and are evaluating the hearing status of TTSP deficient mice using auditory brainstem responses. So far, this strategy has allowed us to identify another TTSP gene causing deafness in mice and to prioritise this specific TTSP plus 3 others for high throughput mutation analysis in sporadic deafness cases and samples from families used to map deafness loci that coincide with proteases. Up to now, we have identified mutations in another TTSP in one deafness patient.

This integrated approach should lead to a comprehensive understanding of the role of this family of serine protease in inner ear function and insights into the pathogenesis of hearing loss, as well as strategies for their prevention and treatment.

Biography

Michel Guipponi completed his PhD studies in 1997 at the Genetics Department, University of Montpellier (France). Moving to the Medical School in Geneva (Switzerland) in 1997, he became involved in different areas of human genetics, successfully participating in the isolation of a new serine protease mutated in both familial and sporadic deafness. In 2001, he received a Research Training Fellowship from the Garnet Passe and Rodney Williams Memorial Foundation to work in the Genetics and Bioinformatics division at the Walter and Eliza Hall Institute. His research project, also supported by a Project Grant from the NH&MRC, aimed to investigate the role of serine protease in deafness; the key approaches being gene expression profiling, candidate gene mutation screening and generation of knockout mouse models.

POLYMERS, NEUROTROPHINS, AND COCHLEAR IMPLANTS: HIGH FIDELITY SOUND

Graeme Clark
Bionic Ear Institute
Victoria

Speech processing has improved significantly with multi-channel cochlear implants by presenting additional of formant and spectral information. There are, however, limitations in hearing speech in noise and music appreciation. Further refinements will require the coding of fine temporo-spatial patterns of stimulation. This will need the preservation of greater numbers of auditory neurons and higher density electrodes. A satisfactory neural population for high fidelity sound can be achieved by preventing neural degeneration using neurotrophins. The in-vivo studies show preservation not only of spiral ganglion cells but peripheral processes, but this only applies as long as the neurotrophin is infused into the scala tympani. Regeneration and resprouting of peripheral processes from residual ganglion cells has also been studied, and has demonstrated that sprouting occurs, but it forms a network in the spiral sulcus, and further research is required to control the direction of growth. The site of action and distribution of the neurotrophins in the cochlea has been researched with radio-labelled neurotrophin (NT-3), and this demonstrates that the greatest proportion of the signal was in the periosteum and decreased from base to apex. To study the mode of action of the neurotrophins retrobeads with neurotrophins adsorbed have been infused into the scala tympani, and the results show only a small amount of neurotrophin present in the auditory nerve and Rosenthal's canal. The neurotrophin may have been picked up by phagocytic cells around the periosteum. To provide a more effective delivery of neurotrophins they have been incorporated into inherently conducting polymers, in particular polypyrrole. The studies show that with galvanostatic polymerization there is effective incorporation, and it can be released using cyclic voltametry over a period of days to weeks. This means that electrodes made with polypyrrole, incorporating neurotrophin could be effective new arrays sited either in the scala tympani or the scala media. There are, however, a number of issues that require solution, particularly: mechanical properties, biocompatibility, long term adhesion, electrical properties, and factors that would allow a scala media placement. Further research is required to optimize these electrode arrays.

Biography

Graeme Clark was appointed Foundation Professor of Otolaryngology at The University of Melbourne in 1970 after completing Master of Surgery/Doctor of Philosophy degrees at the University of Sydney. He is a Fellow of the Royal College of Surgeons Edinburgh and England (FRCS) and the Royal Australasian College of Surgeons (FRACS). In 1983 Professor Clark was awarded the Honour of Officer of the Order of Australia (AO) for services to Medicine. He was awarded Honorary Doctorates of Medicine from the Universities of Hannover (1988) and Sydney (1989). Professor Clark was the Chief Investigator of a National Health & Medical Research Council Program Grant (1984–93), Director of an Australian Research Council's Special Research "The Human Communication Research Centre" (1988–1996), Director of the Cooperative Research Centre for Cochlear Implant, Speech and Hearing Research (1992–1997), Head of the Cochlear Implant Clinic at the Royal Victorian Eye and Ear Hospital (1985-2003), Founder of the Bionic Ear Institute (1985) and has been its Director since that time. Professor Clark was elected an Honorary Member of the Section of Otology of The Royal Society of Medicine, London in 1994 and in 1997 received the Sir William Upjohn Medal from the University of Melbourne. In 1998 Professor Clark was elected a Fellow of the Australian Academy of Science and Fellow of the Australian Academy of Technological Sciences and Engineering. The 1999 Professor Clark was awarded the Victoria Prize for scientific discovery or innovation leading to a major commercial outcome. In 1999, he gave the biennial Joseph Toynbee Memorial Lecture and in 2001, the Graham Fraser Memorial Lecture. Professor Clark was Guest of Honour at the 7th International Cochlear Implant Conference and a keynote speaker at the 8th International Congress Paediatric Otorhinolaryngology. Professor Clark was elected an Honorary member of the American Otological Society, an Honorary Doctorate of Science at the University of Wollongong and given the Aram Glorig Award. In 2003 Professor Clark was awarded an Honorary Fellowship of the Royal Society of Medicine and Honorary Fellow, Royal College of Surgeons, England. He was Guest of Honour and keynote speaker at the 4th Congress of Asia Pacific Symposium on Cochlear Implant and Related Sciences and was awarded an Honorary Doctorate of Engineering at the Chung Yuan Christian University, Taiwan. Professor Clark has recently been awarded a Companion of the Order of Australia (AC) for services to medicine and to science through innovative research to further the development of cochlear implant technology for worldwide benefit.

MOLECULAR BIOLOGY IN HEAD AND NECK CANCER – HOW WELL ARE WE TRANSLATING?

Joseph Califano
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University
USA

Head and neck squamous cell carcinoma has benefited from the application of molecular biologic research to the clinical arena in terms of detection, treatment, and surveillance. This presentation will focus on the application of DNA based discoveries in the detection and surgical treatment of these neoplasms, with particular emphasis on advances in body fluid based detection, suveillance, and surgical therapy for head and neck cancer, as well as the implications of recent discoveries in terms of the etiology of head and neck cancer.

Biography

Dr. Joseph Califano is currently an Associate Professor in the Departments of Otolaryngology - Head & Neck Surgery and Oncology at Johns Hopkins Medical School. He is a graduate of Harvard Medical School in Boston, Massachusetts, and performed his residency at the Department of Otolaryngology - Head & Neck Surgery at Johns Hopkins Hospital, as well as a fellowship in head and neck oncologic surgery at Memorial Sloan Kettering Cancer Center. He is a practicing head and neck surgeon as well as active investigator who described the initial genetic progression model for head and neck cancer development. His current research interests include the molecular biologic basis of head and neck cancer development, with a particular interest in molecular alterations in premalignant lesions, genetic instability, mitochondrial dysregulation, as well as molecular detection and surveillance.

IMMUNOLOGICAL PARAMETERS IN NPC

Denis Moss
Queensland Institute of Medical Research
Queensland

Of all human cancers, the EBV-associated malignancies offer the best opportunity of developing successful immunotherapeutic cures. This optimism is based on the fact that these malignancies display virally defined targets with which to direct immunotherapy. Nasopharyngeal carcinoma (NPC) is of particular importance in this regard. This malignancy is endemic in many parts of Asia with a much lower incidence in developed countries. It has already been established that NPC expresses immunological characteristics that suggest that it might be susceptible to both therapeutic and prophylactic vaccination. With this in mind, we have formulated a vaccine preparation that reflects the proteins expressed in NPC biopsies. This vaccine is based on the patented polytope concept delivered in a replication-deficient strain of adenovirus. Preclinical studies suggest that this vaccine preparation might have both therapeutic and prophylactic benefit in NPC patients. Thus we have demonstrated that suitable mice can be protected from the expansion of quasi NPC cells by vaccination with this formulation. We are currently involved in initiating clinical trials at several sites.

Biography

Professor Denis Moss is Chair of the Therapeutics and Clinical Division at QIMR. His graduate and post-graduate training was done through the University of Queensland. Apart from a year's post-doc experience in 1979 in Tony Epstein's laboratory in Bristol, he has remained at QIMR. His laboratory has a had an interest in immune control of Epstein-Barr virus-associated disease. In recent years he has moved into the area of translational research and is currently investigating immunotherapeutic strategies for EBV driven malignancies.

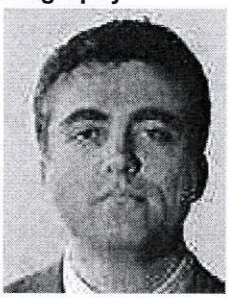
GROWTH FACTORS AND THEIR IMPLICATIONS IN HEAD AND NECK CANCER

Andrew Scott
Tumour Targeting Program
Ludwig Institute for Cancer Research
Victoria

The Epidermal Growth Factor Receptor (EGFR) is an attractive target for tumour-targeted antibody (mAb) therapy in view of its over-expression in many types of epithelial tumours, including head and neck cancers. Overexpression of EGFR is associated with intracellular signalling cascades which lead to increased cancer cell survival, proliferation, invasion and angiogenesis. Antibodies and tyrosine kinase inhibitors (TKIs) against the EGFR (eg C225 and Iressa) have entered the clinic, and have shown impressive results as monotherapy and in combination with chemotherapy and radiotherapy (RT). Both C225 and Iressa has shown efficacy as monotherapy in patients with advanced SCC head and neck in phase II trials. C225 in conjunction with chemotherapy has shown response rates of 15-20% and disease control rates up to 50%. In a recent phase III randomised trial of RT vs C225 & RT in stage III-IV SCC head and neck, C225 and RT showed significantly increased local control and overall survival.

Our laboratory research has focused on the biology and targeting of EGFR. We have developed a novel monoclonal antibody (mAb 806) that binds to both the delta2-7 mutant form of EGFR, and to EGFR expressed by cells exhibiting amplification of the EGFR gene (eg SCCC head and neck), but not to cells or normal tissue expressing the wild type receptor in the absence of gene amplification. The unique specificity of mAb 806 offers an advantage over current EGFR antibodies which all display significant binding to the liver and skin in humans. We have shown that mAb 806 binds to a unique epitope on the EGFR which is exposed in the transitional untethered form of the receptor, which is only expressed on tumour cells. MAb 806 specifically targets U87MG.Δ2-7 and A431 (a cell line expressing > 10^6 EGFR per cell) xenografts grown in nude mice, and in cell cultures is rapidly internalized by macropinocytosis and subsequently transported to lysosomes. The growth of established HN5 xenografts, a cell line from a head and neck carcinoma that endogenously expresses EGFR, was significantly inhibited by mAb 806, as were established U87MG.Δ2-7 and A431 xenografts. Importantly, mAb 806 significantly enhances the tumour inhibitory effects of mAb 528 (which blocks ligand binding to EGFR, similar to C225), and AG1478 (a TKI to EGFR). We have generated a human chimeric form of mAb 806 (ch806) that has similar binding affinity to the unique EGFR epitope, but has more potent immune effector function compared to mAb 806. Ch806 has potent growth inhibitory effects on established xenografts. We have produced ch806 under cGMP conditions in our Biological Production Facility, and clinical trials of ch806 are about to commence in patients with SCC head and neck and lung cancer.

Biography



Andrew Scott graduated in Medicine from the University of Sydney (MB BS - Hons), and trained in Internal Medicine, Nuclear Medicine and Tumour Immunology in Sydney, and at Memorial Sloan-Kettering Cancer Center, USA. His current appointments include Director, Tumour Targeting Program, and Program Head, Clinical Program, Ludwig Institute for Cancer Research, Melbourne Tumour Biology Branch; Director, Centre for PET, Austin Hospital; and Associate Professor, Department of Medicine, University of Melbourne. His research is focused on developing innovative strategies for targeted therapy with monoclonal antibodies and cell signalling inhibition, and in oncology applications in PET, both in staging and biologic characterisation of tumours. A/Prof. Scott has over 110 peer reviewed publications, 10 invited reviews and 10 book chapters principally in cancer research and PET.

CAN GENE TECHNOLOGY IMPROVE THE MANAGEMENT OF HEAD NECK CANCER

William Coman
Professor of Otolaryngology Head and Neck Surgery
University of Queensland
Queensland

We are looking to gene technology to improve the management of head and neck cancer in two major areas. Firstly from the initial tumour biopsy it should be possible to predict tumour behaviour. That is, tumours with good or bad prognosis so that treatment may be tailored accordingly. This should improve the management of head neck cancers in about 40% of cases. From the work at the Princess Alexandra Head and Neck clinic and the Queensland Institute of Medical Research we are well on the way to this objective.

Secondly, gene technology can identify the active proteins which are associated with tumorgenesis, so that it should ultimately be possible to develop antibodies to these proteins. Work is already being carried out with malignant melanoma and prostatic cancer. We are on the threshold of similar studies in cancer of the head and neck.

Biography

Bill was the first Queenslander to be appointed as an examiner to the Court of Examiners of the Royal Australasian College of Surgeons. He also held the positions of Chief Examiner, Chairman of the Surgical Board in Otolaryngology Head and Neck Surgery, and President of the Australian Society of Otolaryngology Head and Neck Surgery. Bill has an international reputation in the field of Head and Neck Cancer surgery and Rhinoplastic surgery. In conjunction with plastic surgeons: Dr David Robinson and Dr David Theile, conducted the first pharyngolaryngectomy, using a jejunal conduit, for hypopharyngeal cancer, which improved the quality of life for patients. This work gained international acclaim. Since then has collected and recorded information on over 300 cases with the best reported survival figures. In 1978, he established, and now chairs, a multi-disciplinary Head and Neck Cancer Clinic at the Princess Alexandra Hospital, with senior colleague, Dr McCafferty, where all consultants and clinicians are involved in discussing each case. Since 1983, Bill has been invited as guest lecturer at 56 national and international meetings, conferences or courses. In 2003, Bill was invited to be the First International Guest Professor for the Society of University Otolaryngologists - Head and Neck Surgeons. In addition to the above, since 1968, he has given presentations at various national and international meetings, conferences or courses on 30 different occasions. Bill has been Lecturer or Clinical Lecturer in Otolaryngology for both clinicians and nurses since 1974 and has held the position of Professor of Otolaryngology, Head and Neck Surgery, within the Department of Surgery at the University of Queensland since 1990. Grants awarded include a $2 million grant for the establishment of a Division of Otolaryngology, Head and Neck Surgery at the University of Queensland.

HIGH-DENSITY MICROARRAY ANALYSIS IN CANCER AND ALLERGY – WHAT CAN BE DECIPHERED FROM TRANSCRIPTIONAL PROFILES?

Carl Borrebaeck
Department of Immunotechnology
Lund University
Sweden

Gene expression profiling has become a promising tool to study disease progression, disease stratification and as a discovery tool to identify new molecular targets for therapy. Today, high density DNA microarrays have been used to study numerous cancers, while less information exist regarding transcriptional profiles in e.g. allergy. We have applied high-density DNA microarray in studies of the molecular mechanisms of disease, in particular focusing on dendritic/T cells in allergy and non-Hodgkins B cell lymphomas.

Dendritic cells (DC) play an important role in the initiation of primary T cell responses and regulation of secondary immune responses. Located at sites of allergen entry, e.g. skin and mucosa, they internalize and process encountered allergens. Thereafter, they migrate to secondary lymphoid organs and present the allergen peptides to T cells, which results in proliferation, Th2 polarization and thus the initiation of an allergic response. DCs and their effect on memory T cells from individuals with lipase or pollen induced allergy have been studied. Monocyte-derived DCs, generated from blood of atopic and non-atopic individuals, were stimulated with allergen and the differential transcriptional profiles of allergen pulsed DCs, as well as T cells, were analyzed with high-density microarray analysis. Peripheral T cells from healthy and allergic donors responded differently after stimulation with allergen-loaded DCs, with respect to cytokine production, proliferation, surface marker expression and gene transcription. We found genes involved in Th2 cell biology, such as genes important for homing, adhesion, signaling and transcription, in addition to genes previously not described in the context of allergy.

Mantle cell lymphoma (MCL) is a non-Hodgkins B-cell lymphoma with a median survival of 3-4 years. The disease is incurable, current treatments are not effective and new approaches to therapy must be sought. In an attempt to understand the etiology of MCL and subsequently to identify novel strategies for immunological intervention we have applied gene expression analysis of 21 MCL tumors. Hierarchial clustering revealed that distinct genetic signatures could be identified for several clinical parameters. MCL is also believed to be derived from a naïve B-cell of the mantle zone, but our expression profiles of various surface antigens, such as immunoglobulin receptors, chemokine receptors and adhesion molecules supports the conclusion that the transformation event takes place during transition from a primary follicle to a germinal center.

Biography

Carl Borrebaeck is chairman of the Department of Immunotechnology, Lund University and received the first chair as professor of Immunotechnology in Scandinavia 1989. His main research interest has been antibody engineering for the generation of human therapeutic antibodies. In the last 5-6 years the interest has focused on deciphering mechanisms behind allergy and B cell cancers, aiming at identify novel approaches for immune intervention. This has been performed by applying DNA microarrays and developing antibody microarrays for high-throughput genome/proteome analysis.

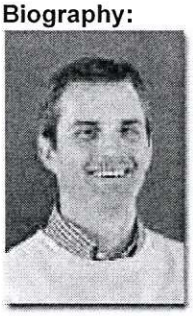
Professor Borrebaeck spent a sabbatical year with Prof. Allen Edmundson at the Oklahoma Medical Research Foundation 1996 and did his post-doctoral training with Prof. Marilyn Etzler at the University of California in Davis. He received his D.Sc. in 1979. He is a member of the Royal Swedish Academy of Engineering Sciences (IVA).

EPITHELIAL MUCINS: ROLES IN MUCOSAL HOMEOSTASIS AND DISEASE

Michael McGuckin
Epithelial Cancer and Mucosal Biology Laboratory
Mater Medical Research Institute
Queensland

Epithelial mucins are very large and complex glycoproteins expressed by all mucosal epithelial tissues. Epithelial mucins can be broadly divided into two classes: secreted gel-forming mucins and cell surface mucins. Secreted gel-forming mucins are the major product of goblet and mucus cells, are the major constituent of mucus and are responsible for the viscous properties of mucus. Gel-forming mucins homo-oligomerise forming huge molecular complexes, the integrity of which is essential for the rheological properties of mucus. Mucus has long been regarded as an essential part of the mucosal barrier to infection, although this is based on very little *in vivo* evidence. Cell surface mucins are expressed on the apical membrane surface of virtually all mucosal epithelial cells. The large extracellular heavily-glycosylated domain of these mucins towers over other molecules in the apical membrane glycocalyx and can be shed from the cell surface. The cytoplasmic domains of cell surface mucins lack kinase activity but contain motifs consistent with a role in signal transduction. Polymorphisms in mucin genes have not been the subject of rigorous investigation largely due to their size and complexity. However, polymorphisms have been associated with inflammatory respiratory diseases, gastritis, inflammatory bowel diseases and infertility. The central hypothesis being pursued by our laboratory is that both secreted and cell surface mucins are a critical element of the mucosal barrier to infection, and that, rather than being a static barrier, mucins modulate host responses to infection and in turn are modulated in composition by both innate and adaptive immunity. Our laboratory has identified several novel cell surface mucin genes and we have developed novel murine models of mucin deficiency that illustrate the importance of mucins in gastrointestinal defence. We have demonstrated initiation of intracellular signalling by cell surface mucins in response to bacteria and are exploring the downstream consequences of this signalling. Expression of both secreted and cell surface mucins are clearly modulated by a range of inflammatory cytokines. We are now using mass spectrometry-based glycomic techniques to demonstrate that the glycosylation of mucins can also be altered by the immune system. Whilst mucins are an essential component of mucosal defence it is manifest that defects in the mucins themselves, or in regulatory mechanisms governing their composition and production, can lead to chronic inflammatory and obstructive conditions such as those commonly facing the clinical otorhinolaryngologist. Potential novel therapeutic strategies to alleviate these conditions will be discussed.

Biography:



Dr McGuckin first became involved in biomedical research following completion of his PhD research in 1987. He is the author of over 50 papers in international peer-reviewed journals, and an inventor on 3 patents. From 1988 until 1991 he worked to help develop, and assess in clinical management, mucin-based blood diagnostic tests for ovarian and breast cancers now used in Australia and internationally, work published in leading clinical journals. Dr McGuckin is an author of three reviews on mucin-based serum diagnostic assays. From 1992, Dr McGuckin received NHMRC funding and began independent studies of tumour-associated mucins. This phase coincided with a growth in knowledge of the mucin genes, and a growing interest in the biology and clinical applications of the MUC1 mucin in particular. Over the next three years Dr McGuckin published in both clinically oriented and basic oncology journals and developed broad skills in cellular and molecular biology. From 1995, he became the CIA on an NHMRC grant, published diagnostic studies in clinical journals, several major basic studies of mucins in carcinomas, and became involved in distinct collaborative studies in ovarian cancer. In 1998 he was awarded his third successive NHMRC grant, expanded his research team and further refined and developed the focus of his research on the cell and molecular biology of epithelial mucins. His studies now encompass a key focus on examination of cell surface mucins in the innate immune system, the identification and characterisation of novel cell surface mucin genes, examination of mucin expression and biology in epithelial diseases including cancer, basic cell biology studies and some diagnostic research. Dr McGuckin now has a major molecular program in his laboratory and his team has identified and characterised three novel human mucin genes.

In 1999 Dr McGuckin successfully moved his research team to the newly formed Mater Medical Research Institute (MMRI), which has a niche focus complementing the interests of his research program. Dr McGuckin has assembled a highly skilled research team and developed the necessary local, national and international collaborations. Dr McGuckin's current international reputation is exemplified by invitation to: the international workshop Mucins in Health and Disease (Cambridge, 2000), 14th Annual North American Cystic Fibrosis Conference (2000), Carbohydrates and the Immune Response (Greece, 2001), his invitation to provide a chapter Mucin Detection and Quantitation in the Methods in Molecular Biology series published in 2000, his invitation to provide both the chapter for Leucocyte Typing VII and the Protein Reviews on the Web entry for CD227 (MUC1). He regularly reviews manuscripts for a broad range of international journals including TIBS, J Biol Chem, Nature Reviews Cancer, Int J Cancer, Cancer, Br J Cancer, Tumor Biol, Gut, J Pathol, Mol Cell Endocrinol, Am J Obstet Gynecol. He regularly reviews research grants for the NHMRC, Australian Cancer Councils and charitable cancer foundations and NZ HRC. In 2001 and 2002 he served on the National Health and Medical Research Council Grant Review Panel for Oncology.
In 2000 Dr McGuckin was appointed as an Adjunct Associate Professor by the Univ of Qld Faculty of Health Sciences. Locally, he is an active member of the medical research community chairing the Qld Medical Research Week Organizing Committee for the Australian Society for Medical Research (2001-2) and serving on the Brisbane Immunology Group Committee (2002-3); he is also an elected National Director of the ASMR (2001-5). Dr McGuckin is chairperson of the Mater Hospitals Biosafety Committee, and serves on the Univ of Qld Faculty of Health Sciences Animal Experimentation Ethics Committee, Mater Hospitals Research Support Committee, Mater Hospitals Ethics Committee Scientific Sub-Committee, and the MMRI Executive Leadership, Post-graduate Student, and Facilities Committees. In 2002 he was appointed to head the Epithelial Cancer and Mucosal Biology Laboratory at the MMRI, which hosts his Mucin Research Team and the Inflammatory Bowel Disease Team lead by Assoc Prof Timothy Florin.

GENETIC DETERMINANTS IN NASAL AND SINUS DISEASE

William Smith
Clinical Immunology and Allergy
Royal Adelaide Hospital
South Australia

A range of factors contribute towards chronic sinus disease and some cases appear predominantly idiopathic. Allergy may be an underlying factor in some patients; the underlying tendency to develop allergies, or "atopy", is a strongly genetic trait, but despite intense study, a clear genetic pathway has not been elucidated. Nasal polyposis (polypoid rhinosinusitis) is an enigmatic condition, usually independent of atopy, and whilst it is related to other disorders in some cases (fungal infection, cystic fibrosis), often no causal factors are apparent. There is an intriguing relationship between polyposis, asthma (usually non-allergic, adult onset type) and aspirin sensitivity, but whilst this triad is well-recognised, the biochemical basis for it is not known, and although this appears to be an acquired condition, it is unclear whether there is a constitutional basis. A few studies have indicated that polyposis may be a familial disorder, and indeed this is the experience of clinicians. However, only a small number of studies have addressed the possibility of a genetic basis, without any conclusive results as yet. The biology of polyposis has received somewhat more detailed study, and many inflammatory cells, cytokines and regulatory factors have been shown to be involved. Methods of investigating the genetics of polyposis including the candidate gene approach and linkage analysis will be discussed.

Biography

Dr William Smith is a specialist in Clinical Immunology and Allergy, based at the Royal Adelaide Hospital. He completed a Ph.D in "Leukocyte Transmigration in Inflammation" at the Hanson Centre, and postdoctoral research in London and Perth. Current research interests include mechanisms of chronic polypoid rhinosinusitis, fungal allergy, and food allergy. Clinical interests include immunotherapy for allergic disease, and aspirin desensitisation.

IMMUNE RESPONSES IN FUNGAL SINUS DISEASE AND THEIR IMPLICATIONS FOR TREATMENT

Peter-John Wormald
Queen Elizabeth Hospital
South Australia

Chronic sinusitis is defined as a group of symptoms (nasal obstruction, rhinorrhoea, post nasal drip, facial pain/headache and loss of smell) present for longer than 3 months. In the immune competent patient, these symptoms can be caused by a large variety of pathologies including chronic bacterial sinusitis, allergic fungal sinusitis, nasal polyposis, chronic fungal sinusitis and patients with asthma and aspirin sensitivity. Currently these conditions are all loosely grouped under the title "Chronic rhinosinusitis (CRS)" when it is quite apparent that they have different aetiologies and different prognosis. A recent hypothesis regarding the aetiology of CRS was proposed in 1999 by the Mayo Clinic who stated that fungus was found in all patients with the diagnosis of chronic sinusitis and postulated that fungal antigens play a significant aetiological role in patients with chronic sinusitis. In order to assess this role we performed a prevalence study which showed that fungus was found in 26% of patients undergoing surgery for CRS. We went further and researched this group and established that both in terms of revision surgery and symptoms, this group had a worse prognosis. We also developed and have published a new classification for fungal sinus disease. This new classification is based on both immunological and laboratory findings. In order to further understand this poor prognostic group of patients we have began to examine both the acquired and innate immune systems and their interaction with fungal antigens. In our department Dr Pant in her PhD thesis has examined the role of fungal specific IgE, IgA, IgG1, 2, 3 and 4 in the various categories of fungal sinusitis and compared these to normal controls and to disease controls (allergic rhinitis patients and patients with CRS without eosinophilic mucin). She has shown that IgE does not play a role as was previously thought in the pathogenesis of allergic fungal sinusitis (AFS) or AFS-like patients. She has also shown very interesting new data that there may be a significant role for IgG3 as this was the only fungal specific immunoglobulin elevated in patients with eosinophilic mucin compared to both controls and diseased controls. It is thought that IgG3 may act as a superantigen and cause significant amplification of the immune system. Dr Tan (Chief Scientist in our department) and Dr Ooi in his PhD thesis has been examining the role of the innate mucosal defence system and theri interaction with both bacteria and fungi. Dr Tan has studied the interaction of fungal antigens with ß-defensins with particular reference to how these defensins interact with mast cells and alter the expression of matrix metalloproteinases (MMPs). MMPs are thought to alter the basement membrane and allow protrusion of the lamina propria with polyp formation. Dr Ooi has examined Cathelicidins and mucosal surfactant and found that these important local immune defence mechanisms are unregulated in patients with CRS and AFS.
In conclusion this research is aimed at understanding the pathogenesis of the group of conditions that make up CRS. This greater understanding of this group will allow better treatments (both medical and surgical) to be developed for each specific group and allow surgeons to better prognosticate for patients of these various groups.

Biography

PJ Wormald has pursued an academic career over the last 10 years. After doing fellowships in the United Kingdom with Prof. George Browning, he spent time as a senior lecturer with Prof. Sellars at the University of Cape Town and as an Associate Professor with Prof. van Hasselt in Hong Kong. During this time he has written 3 books and 5 chapters and published over 75 peer-reviewed articles.
In June 1998 he took up the Chair of Otolaryngology Head & Neck Surgery which is a combined appointment between the Adelaide and Flinders Universities. He has a specific interest in Rhinology and in endoscopic sinus surgery (ESS) and has built a national and international reputation in this field. Over the past 10 years he has been invited to speak at over 25 ESS courses around the world. In addition he has been invited to speak as the key-note speaker to a large number of national and international meetings on various rhinological topics. As part of his rhinological research program, Prof. Wormald has put together a research team that has successfully developed the sheep as an animal model to research various aspects of nasal disease and surgery. This model overcomes some of the major drawbacks of the other models currently in use in that the same instruments and techniques can be used in the sheep as is used in humans. This model has been validated and early work published. The sheep develops an eosinophilic rhinosinusitis with an infestation with the oestrus

ovi parasite that closely approximates the eosinophilic rhinosinusitis seen in patients. This allows research into how the eosinophils interact with the nasal mucosa and how they cause disease. In addition he has developed the animal model to assess the effects of reflux on the upper airway. In combination with the WCH he has developed a unique 4-channel 24 hr pH probe which is able for the first time in the world to be able to reliably assess reflux into the hypophaynx and nasophaynx. He is also developing a series of new surgical techniques and instruments and has a particular interest in endonasal DCR surgery, orbital and optic nerve surgery.

RESHAPING LIFE WITH STEM CELLS

Ross Coppel
Department of Microbiology
Monash University
Victoria

As the western world ages, baby boomers desperately seek a means to preserve their youth. At the same time, degenerative diseases of various organ systems represent major causes of morbidity and mortality in our society and their amelioration consumes a large fraction of the health budget. Of the various technologies that could be used to reverse or slow degenerative disease, stem cells are perhaps one of the most promising as well as one of the most hyped. We are still at an early stage of our understanding of how stem cells function and many of the genomic technologies, such as microarrays and proteomics, used to understand gene function are being applied to this problem. This lecture will examine the current state of stem cell work in a number of areas and discuss key issues that need to be elucidated before the promise of this technology can be realised.

Biography:

Ross Coppel is Professor of Microbiology within the Medicine, Nursing and Health Sciences Faculty at Monash University. His laboratory is involved in research into malaria, tuberculosis, autoimmunity and bioinformatics.

Ross is a Howard Hughes Medical Institute International Fellow and an internationally recognised scientist in the fields of the molecular biology of malaria and primary biliary cirrhosis. In 2002 a Third Edition of the book, Reshaping Life, a Guide to Genetic Engineering for the Layperson, Nossal, G.J.V. and Coppel, R.L. was produced. He is a member of an advisory committee that oversees Bioinformatics of the malaria genome project and administers the malaria sequence database for the World Health Organisation. Funding to support his research activities comes from national and international agencies including the National Health & Medical Research Council, the Australian Research Council, the Wellcome Trust, the National Institutes of Health, the United States Agency for International Development, the World Health Organisation and the Bill and Melinda Gates Foundation. In 2003 Ross co-founded Glykoz to commercialise new antibiotics that he and his collaborators have discovered

NEW DISCOVERIES IN THE PROGRESSION OF HEAD AND NECK CANCER

Joseph Califano
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University
USA

The long latency period between exposure to viral or chemicalcarcinogens and the development of head and neck squamous cell carcinomaunderscores the importance of carcinogenesis and the biology of precancerous mucosal disease. This presentation will focus on recent molecular biologic advances in the understanding of premalignant disease of the head and neck, and the implications for therapy and detection of head and neck cancer.

Biography

Dr. Joseph Califano is currently an Associate Professor in the Departments of Otolaryngology - Head & Neck Surgery and Oncology at Johns Hopkins Medical School. He is a graduate of Harvard Medical School in Boston, Massachusetts, and performed his residency at the Department of Otolaryngology - Head & Neck Surgery at Johns Hopkins Hospital, as well as a fellowship in head and neck oncologic surgery at Memorial Sloan Kettering Cancer Center. He is a practicing head and neck surgeon as well as active investigator who described the initial genetic progression model for head and neck cancer development. His current research interests include the molecular biologic basis of head and neck cancer development, with a particular interest in molecular alterations in premalignant lesions, genetic instability, mitochondrial dysregulation, as well as molecular detection and surveillance.

EVOLUTION OF THE ANATOMY AND FUNCTION OF THE LARYNX

William Coman
Professor of Otolaryngology Head and Neck Surgery
University of Queensland
Queensland

The larynx developed initially as a primitive sphincter. We now consider its main evolutionary roll is it use in the transfer of information from one human being to another. While cancer can be induced experimentally in the animal larynx model, in the natural state it is exclusively a disease affecting the human species.

Radiotherapy is the gold standard for the treatment of early laryngeal cancer. Of recent years Laser Microlaryngeal surgery has improved outcomes in disease control and voice.

Sir Richard Doll has demonstrated that the correct scientific solution to comparing the efficacy of treatment modalities is by the double blind perspective randomised controlled trial. This paper will present an update of such a trial.

Biography

Bill was the first Queenslander to be appointed as an examiner to the Court of Examiners of the Royal Australasian College of Surgeons. He also held the positions of Chief Examiner, Chairman of the Surgical Board in Otolaryngology Head and Neck Surgery, and President of the Australian Society of Otolaryngology Head and Neck Surgery. Bill has an international reputation in the field of Head and Neck Cancer surgery and Rhinoplastic surgery. In conjunction with plastic surgeons: Dr David Robinson and Dr David Theile, conducted the first pharyngolaryngectomy, using a jejunal conduit, for hypopharyngeal cancer, which improved the quality of life for patients. This work gained international acclaim. Since then has collected and recorded information on over 300 cases with the best reported survival figures. In 1978, he established, and now chairs, a multi-disciplinary Head and Neck Cancer Clinic at the Princess Alexandra Hospital, with senior colleague, Dr McCafferty, where all consultants and clinicians are involved in discussing each case. Since 1983, Bill has been invited as guest lecturer at 56 national and international meetings, conferences or courses. In 2003, Bill was invited to be the First International Guest Professor for the Society of University Otolaryngologists - Head and Neck Surgeons. In addition to the above, since 1968, he has given presentations at various national and international meetings, conferences or courses on 30 different occasions. Bill has been Lecturer or Clinical Lecturer in Otolaryngology for both clinicians and nurses since 1974 and has held the position of Professor of Otolaryngology, Head and Neck Surgery, within the Department of Surgery at the University of Queensland since 1990. Grants awarded include a $2 million grant for the establishment of a Division of Otolaryngology, Head and Neck Surgery at the University of Queensland.

MUSCLE STEM CELLS AND GENE EXPRESSION: SOME SURPRISES FROM THE LARYNGEAL MUSCLES

Ann Trezise
School of Biomedical Sciences
University of Queensland
Queensland

Adult skeletal muscle is a stable, post-mitotic tissue with very little turnover of nuclei. However, muscle injury results in myofiber necrosis and degeneration, rapidly followed by regeneration characterised by the activation of myogenic cells to proliferate, differentiate and fuse to form new multinucleated myofibers. The regenerative capacity of skeletal muscle is finite, dependent on a resident population of muscle satellite cells and recapitulates the myogenic regulatory factor (MRF) directed program of embryonic myogenesis. This widely held view of the nature of adult skeletal muscle is based almost exclusively on the analysis of limb muscle, but is assumed to apply equally to all skeletal muscle. Our analysis of a number of head and neck muscles, including tongue and intrinsic laryngeal muscles, has shown that these muscles march to a different tune. Using both molecular and functional techniques, all our analysis indicates the presence of continuous myoblast proliferation in the extraocular, masseter, tongue and intrinsic laryngeal muscles, in the absence of overt injury and necrosis. Compared to hindlimb muscle, head and neck muscles express high levels of the myogenic regulatory factors Myf5 and MyoD. In trunk and limb muscles significant Myf5 and MyoD expression is only seen in proliferating myoblasts during embryogenesis or active muscle repair. In addition to expressing Myf5 and MyoD, head and neck muscles express "immature" isoforms of myosin heavy chains, have increased permeability to Evans Blue Dye and undergo DNA synthesis as evidenced by incorporation of bromo-deoxyuridine. One of the implications of these findings is that the finite proliferative capacity of the trunk and limb muscle satellite cells does not apply to the cells that provide a life long source of proliferating myoblasts to head and neck muscles. Our future work aims at understanding the molecular basis for the continuous myoblast proliferation in the intrinsic laryngeal muscles and other head and neck muscles.

Biography

AnnTrezise returned to Australia in 1996 having spent 7 years overseas as a Postdoctoral Fellow. My first position was at the Hospital for Sick Children (Toronto) as a Canadian Cystic Fibrosis Foundation Postdoctoral Fellow. I was then awarded a Beit Trust Senior Postdoctoral Fellowship and worked at the Weatherall Institute of Molecular Medicine (Oxford) where I continued my work on cystic fibrosis and began work on understanding how cells coordinate the expression of many genes by showing that the CF gene is coordinately regulated with the MDR1 gene. Increased expression of the MDR1 gene is responsible for most tumours developing resistance to chemotherapeutic drugs. I took up my current position as Senior Lecturer in the Dept. Anatomy & Developmental Biology at the University of Queensland in 2000. My research continues to focus on how the cells of higher eukaryotic organisms, such as mammals, coordinate the expression of 1000's of genes in each nucleus. We have also begun investigating the molecular basis of the specialised nature of head and neck skeletal muscle, in particular the intrinsic laryngeal muscles. My research papers have received in excess of 1000 citations and I currently hold two ARC Discovery Project grants.

SENSORY CELL DEATH AND REGENERATION IN THE COCHLEA

Yehoash Raphael
Kresge Hearing Research Institute
University of Michigan
USA

Cochlear hair cell loss is irreversible, leading to permanent hearing impairment. To provide a biological restoration of hearing, it is necessary to generate new hair cells to replace the ones that are lost. One strategy for replacing lost hair cells is to introduce cells into the cochlea that are engineered to integrate in the sensory epithelium and differentiate into new functional hair cells. An alternative strategy is to transdifferentiate non-sensory cells that remain in the deaf cochlea into new hair cells. Following the latter strategy, we have used gene transfer methods to manipulate gene expression in cochlear supporting cells in an attempt to induce their transdifferentiation into new hair cells.

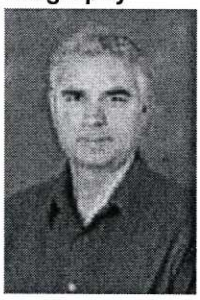
Math1, the mouse homolog of the *Drosophila* gene *atonal* is necessary for hair cell development. We inoculated an adenovirus vector with the *Math1* gene insert into the scala media of deafened guinea pigs and determined that non-sensory cells expressed *Math1*. Several weeks later, new hair cells were detected in the area of the organ of Corti and in adjacent epithelial regions. Auditory nerve fibers were observed to grow in the direction of the new hair cells. Two months after the gene transfer procedure, animals that initially had no measurable ABR thresholds exhibited responses to signals that were 20-30 dB better than the "no response" intensity.

To increase the number of new hair cells, we combined the *Math1* gene therapy with over-expression of *Skp2*, an F-box protein which causes G1 to S transition through ubiquitination of $p27^{Kip1}$. The combined therapy resulted in generation of new supporting cells and in the generation of a higher number of new hair cells in the cochlea.

The possibility for generating new cochlear hair cells in the mature organ of Corti provides compelling and encouraging evidence for further exploration of the use of gene transfer technology to replace lost cochlear hair cells, and raises hope that clinical applicability will become a reality in the future. The technology for generating new cochlear hair cells should also be explored in the vestibular epithelium for treatment of balance disorders.

Supported by the GenVec and NIH/NIDCD Grants R01 DC 01634 and DC05401, and P30 grant DC 05188.

Biography



Yehoash (pronounced Yoash) is an inner ear biologist with educational background in audiology and basic biology. He has been on the Faculty of the Kresge Hearing Research Institute at the University of Michigan since 1990 and is currently the Director of the Otopathology Laboratory. In recent years, Yoash's research has been focused on developing gene therapy for protection repair and regeneration in the inner ear. The work involves both the auditory and the vestibular portions of the ear. The work has shown that introducing foreign genes into the inner ear can help protect hair cells and spiral ganglion neurons against degeneration. Recent work using adenovirus-mediated gene therapy has pioneered the ability to grow new hair cells in the living mammalian cochlea. The lab is also engaged in analyzing the structure of the inner ear of mutant mice with auditory or vestibular deficits. Future goals of the projects in the Otopathology Laboratory are to (a) design gene therapy technology for treating hereditary inner ear disease, (b) enhance the ability to generate new cochlear hair cells to accomplish recovery of structure and function of the pathological inner ear and (c) improve cochlear implant function by increasing the biocompatibility of the prosthesis.

CELL AND DRUG-BASED THERAPIES IN THE DEAFENED COCHLEA: NEW STRATEGIES FOR COCHLEAR IMPLANTATION

Robert Shepherd
Department of Otolaryngology
University of Melbourne
Victoria

A sensorineural hearing loss (SNHL) initiates ongoing degeneration of spiral ganglion neurones (SGNs), the target neurones for cochlear implants. The degenerative changes observed are associated with a loss of peripheral processes and demyelination of the soma of surviving auditory neurones[1]. These changes have been shown to affect neural response properties to electrical stimulation, including elevated thresholds, a reduction in the security of action potential propagation and altered refractory properties[1]. Deafness induced degeneration of SGNs may adversely affect the clinical performance of implant subjects, as evidenced by the strong negative correlation between duration of deafness and speech perception[2]. Moreover, the SGN degeneration may place limitations on the development of more advanced cochlear implants.

Our research has been directed toward developing cell and drug-based therapies for SGN rescue or regeneration. Chronic delivery of the neurotrophin brain-derived neurotrophic factor (BDNF) in deafened guinea pig cochleae showed significant rescue of SGNs and a reduction in electrical thresholds compared to deafened controls. Importantly, SGN survival was even greater in animals where BDNF was combined with chronic electrical stimulation (ES), while ES alone could not maintain a trophic influence on these neurones. We have also shown that BDNF rescues SGNs in the deafened rat cochlea, providing further support for the efficacy of this neurotrophin. Taken together, these findings support a potential clinical application for BDNF in treating SNHL.

Cell-based therapies offer both cell rescue and regenerative strategies that also have potential clinical application. We are currently investigating Schwann and stem cell-based therapies for this purpose. Xenotransplantation experiments delivering rat Schwann cells into the scala tympani of deafened guinea pigs showed small but significantly enhanced SGN survival following two weeks in the basal turn of treated cochleae compared with controls. This is consistent with findings that Schwann cells contribute to peripheral neurone maintenance. We have also commenced studies directed towards SGN regeneration by the transplantation of stem cells (SC) that may - under the appropriate conditions - differentiate into functional neurones. To date we have examined the survival and migration of partially differentiated SCs following xenograft transplantation into the scala tympani of deafened guinea pigs. The transplanted SCs survived the maximum implant period of four weeks and migrated through all turns of the scala tympani and vestibuli; small numbers were also evident in the modiolus. Importantly the SCs did not evoke an inflammatory response. Future studies will be directed towards optimizing SC differentiation and cell delivery techniques. This includes consideration of the micropores found in the osseous spiral lamina as an important route for the passage of both drugs and cells from the scala tympani into Rosenthal's canal[3].

[1] Shepherd R, Hardie N (2001) *AudiolNeuroOtol,* **6**: 305-318. [2] Blamey et al. (1996) *AudiolNeuroOtol,* **1**: 293-306. [3] Shepherd R, Colreavy M (2004) *Arch Otolaryngol HNS,* **130**: 518-523. *This work was funded by the NIDCD (N01-DC-0-2109 and N01-DC-3-1005).*

Biography

Rob Shepherd is head of the Neurobiology laboratory at the Bionic Ear Institute and an Associate Professor in the Department of Otolaryngology, University of Melbourne. His research has focused on design and safety of cochlear implants and the application of neurotrophins and cell-based therapies with cochlear implants to help protect auditory neurons from degeneration. His research also examines the functional effects of deafness and the plasticity of auditory neurones following reactivation via a cochlear implant. Rob was a Garnett Passe and Rodney Williams Senior Research Fellow from 1996-2000 and is currently the Royal Victorian Eye and Ear Hospital's Wagstaff Fellow in Otolaryngology.

CELL-BASED THERAPIES FOR HEARING LOSS

Michelle de Silva
Bionic Ear Institute
Victoria

Hearing loss is the most common sensory condition in our population often resulting from inner ear hair cell degeneration due to genetic abnormalities or environmental insults. With the availability of pluripotent embryonic stem (ES) cell lines from mice and humans it now possible, in principle, to generate all adult tissue types *in vitro* and to assess the efficacy of cell replacement strategies using animal models. Our aims therefore are twofold. Firstly, to identify factors required for hair cell regeneration and secondly to assess the therapeutic potential of these cells using mouse, guinea pig and rat models for deafness.

Wholesale conversion of ES cells to neurectoderm precursors has the potential to significantly increase the efficiency with which hair cells may be generated *in vitro*. We hypothesise that factors present in the media of established hair cell lines will promote differentiation of neurectodermal cells to inner ear hair cells. We have prepared media supplemented with varying concentrations of the conditioned media from both proliferating and differentiating hair cell lines isolated from the Immortomouse to culture ES cells. Several growth culture conditions, exposure to EGF, BDNF, NT-3, aFGF and bFGF both singly and in combination have also been selected for the examination of gene expression variations as the ES cell population moves along the differentiation pathway. Expression of specific markers of early hair cell development (*Brn3.1*, *Myo6*) and differentiated cell types (*α9 AchR, Myo7a*) have been assessed. ES culture conditions which lead to expression of hair cell markers were characterised in further detail using *in situ* hybridisation and immunohistochemistry to identify hair cell precursors and their differentiated derivatives.

A number of studies have focussed on the delivery of transgenes and growth factors to the inner ear of deaf animals with the aim of regenerating hair cells *in situ*. Although these experiments have been successful in cochlear explants, little success has been achieved with this method *in vivo*. Much of the problem may be due to the difficulties of targeting the factors to the correct location within the organ of Corti in the inner ear. We are testing the ability of mouse stem cells at different stages of differentiation to survive and integrate in the normal and deafened guinea pig cochlea. It is hoped that successful integration and differentiation of these cells may lead to functional restoration by replacing or regenerating cochlear hair cells. Mouse embryonic stem cells have been delivered to the cochlea of one normal and four deaf guinea pigs. The deafening was induced by aminoglycoside antibiotics which destroy hearing function by specifically causing the death or damage of cochlear hair cells. Stem cells were injected directly into the scala media within the cochlea, which contains the hair cells. Integration of the cells into the cochlea is determined using histochemical techniques on cochlear sections.

Biography

Michelle de Silva is a senior postdoctoral research fellow in the Gene Identification and Expression Group at the Murdoch Childrens Research Institute (MCRI). She was awarded her PhD by the University of Melbourne, training as a cell and molecular biologist at the Austin & Repatriation Medical Centre and the Peter MacCallum Cancer Institute. Her PhD involved mapping a chromosomal abnormality associated with multidrug resistance in a human leukaemia cell line. Following her PhD she joined the Gene Discovery Group at the MCRI successfully running a very complex project (genetics and cell biology of attention deficit hyperactivity disorder) a part of the Collaborative Research Centre for the Discovery of Genes for Common Human Diseases. Her work resulted in an International Application under the Patent Co-operation Treaty for genes involved in behavioural disorders. At the end of 2001 she moved to the Gene Identification and Expression Group where she has established the present project involving stem cells and their potential use in understanding and treating hearing loss.

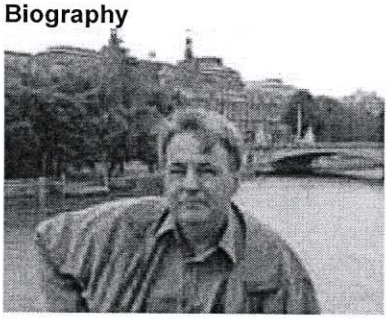
ELECTROPHYSIOLOGICAL ASSESSMENT OF VESTIBULAR FUNCTION

James Colebatch
Department of Neurology
Prince of Wales Hospital
New South Wales

Traditionally, assessment of vestibular function has been heavily dependent upon the vestibular-ocular reflex effects arising from the lateral semicircular canal. Otolith function has been difficult to assess and is likely to be more relevant to the postural role of vestibular afferent signals. In 1994 Colebatch et al. reported the properties of VEMPs (vestibular evoked myogenic potentials), evoked by loud clicks. Evidence since then has accumulated indicating that this reflex originates from the saccule. Additional methods of evoking activity in this pathway have been developed, including tapping the head, bone conducted stimulation and short duration electrical stimulation. These methods represent a new form of vestibular investigation, and, in the case of clicks, one which is dependent upon otolith function. The different methods stimulate the reflex pathways at distinct levels and allow more accurate localization. These techniques are being widely applied and can provide important information in a variety of different otological disorders. A recent case report will be used to illustrate the practical application of such investigations.

Colebatch JG, Halmagyi GM, Skuse NF (1994). Myogenic potentials generated by a click-evoked vestibulocollic reflex. *J Neurol Neurosurg Psychiatry*, 57:190-197.

Biography



Associate Professor Colebatch is currently the head of the Departments of Neurology and Clinical Neurophysiology, Prince of Wales Hospital, Sydney. He graduated in medicine from the University of New South Wales in 1979, trained at the Prince Henry and Prince of Wales Hospitals in Neurology and completed a PhD in 1987. He was the Australasian Registrar at the National Hospitals for Nervous Diseases, London, in 1987 and then was a CJ Martin Travelling Fellow of the National Health and Medical Research Council of Australia, working at the MRC Human Movement and Balance Unit and MRC Cyclotron Unit in London. He was appointed a staff specialist at the Prince Henry and Prince of Wales Hospitals group in 1992. His research interests are in disorders of human motor control and vestibular function.

DESIGNING THERAPEUTIC ANTIBODIES

Carl Borrebaeck
Department of Immunotechnology
Lund University
Sweden

Antibodies have been proposed as the magic bullet of biological immunotherapy for over a century. The success of this particular molecule in the clinic is, however, less than 10 years old and it is only within the last five years that antibodies can be considered as a realistic pharmaceutical agent (1). Today over one hundred antibodies are in clinical trials against numerous indications. The reasons for this late onset of antibody-based immunotherapy are many, but two major ones are, (i) the inherent difficulties in making true human antibodies and (ii) the late disease stages that were accessable for clinical trials. Today the generation of human therapeutic antibodies is solved, from a scientific point of view, and the design is based on recombinant antibody libraries, where in essence all specificities can be harbored conveniently packaged in a filamentous phage. Library sizes of $>10^{11}$ individual antibodies are constructed, which by far exceeds the capacity of the human humoral immune system.

The talk will describe the generation of a human antibody library (2) (n-CoDeR) based on one single molecular scaffold resulting in a specificity space that goes beyond what Nature can provide, resulting in some distinct advantages from a therapeutic point of view. Pre-clinical applications in atherosclerosis, cancer and infectious disease will be discussed including the requirements necessary for clinical trials.

1. Borrebaeck CAK and Carlsson R (2001) Human therapeutic antibodies. **Curr. Opinion Pharmacol**. 1, 404-408.
2. Söderlind E, Strandberg L, Jirholt P, Kobayashi N, Alexeiva V, Åberg AM, Nilsson A, Jansson B, Ohlin M, Wingren C, Danielsson L, Carlsson R and Borrebaeck CAK (2000) Recombining germline-derived CDR sequences for creating diverse single-framework antibody libraries **Nature Biotech.** 18, 852-856.

Biography

Carl Borrebaeck is chairman of the Department of Immunotechnology, Lund University and received the first chair as professor of Immunotechnology in Scandinavia 1989. His main research interest has been antibody engineering for the generation of human therapeutic antibodies. In the last 5-6 years the interest has focused on deciphering mechanisms behind allergy and B cell cancers, aiming at identify novel approaches for immune intervention. This has been performed by applying DNA microarrays and developing antibody microarrays for high-throughput genome/proteome analysis.

Professor Borrebaeck spent a sabbatical year with Prof. Allen Edmundson at the Oklahoma Medical Research Foundation 1996 and did his post-doctoral training with Prof. Marilyn Etzler at the University of California in Davis. He received his D.Sc. in 1979. He is a member of the Royal Swedish Academy of Engineering Sciences (IVA).

OLFACTORY NEURAL STEM CELLS: A FAST MOVING STORY

Anne Cunningham
School of Women's and Children's Health
University of New South Wales
New South Wales

Over the past decade, neuroscientists have confirmed that neurogenesis occurs in discrete areas of the adult brain and spinal cord overturning the long-held dogma that the CNS cannot generate new neurones or renew and repair itself. Neural stem cells (NSCs) are the self-renewing, multipotent cells that generate neurones, astrocytes, and oligodendrocytes in the CNS. There is escalating interest in NSCs from both the aspect of basic developmental biology, which has yielded some major surprises, and their potential therapeutic applications. The olfactory neuroepithelium has been understood for decades to harbour a unique neural progenitor cell as it avidly supports neurogenesis throughout adulthood and is capable of reconstituting cells of neuronal and non-neuronal lineages after injury. Despite intense interest, the exact identity of this cell has eluded olfactory neuroscientists.

To identify this unique cell *in vitro,* we have developed a neurosphere culture system of olfactory progenitor cells and have used a combination of timelapse videomicroscopy on living cells and antibody labelling techniques to characterise its properties. Our recent work has confirmed the multipotent developmental potential of this neural progenitor cell and allowed direct comparison with NSCs from central brain regions. Our system of clonal neurospheres provides a model of progenitor cell and neuronal differentiation that will allow better understanding of the earliest stages of olfactory neurogenesis. Future application of this new knowledge holds promise for novel treatment strategies for the damaged and diseased olfactory system.

Supported by the Garnett Passe and Rodney Williams Memorial Foundation

Biography

Anne Cunningham is Professor of Paediatrics at the University of New South Wales and Director of Research and Head of the Developmental Neurosciences Program at Sydney Children's Hospital. She is a practising Consultant Neurologist, at Sydney Children's Hospital. She trained in medicine and Paediatric Neurology at the University of Sydney and the Royal Alexandra Hospital for Children. Her PhD was undertaken in developmental neuroscience in the area of synaptogenesis at the Children's Medical Research Foundation and subsequently she was a Research Associate at the Howard Hughes Medical Institute, Johns Hopkins University in Baltimore, MD, USA. She joined the faculty at Johns Hopkins in the Department of Molecular Biology and Genetics and was appointed Assistant Professor of Neurology. At Johns Hopkins she worked in the Molecular Olfactory Group headed by Professor Randall Reed, a team that identified many key genes involved in olfactory signal transduction and olfactory neuronal function. She subsequently spent six years as Head of the Sensory Neurobiology Group at the Garvan Institute of Medical Research, before taking her current position at UNSW.

She has worked in the field of olfactory neurobiology for 15 years. Her longstanding interest is in neuronal growth factors, stem and progenitor cells and functional development of the olfactory sensory system. She was the first to describe an IP3 receptor localised to olfactory cilia implicating it with a role in olfactory signal transduction and she made the first immunolocalisation of an odorant receptor to cilia. She has described novel techniques of growing olfactory neurones in culture and was the first to implicate the growth factors GDNF, BDNF and CNTF, with potential functions in olfactory neurogenesis and differentiation. Recently, her description of nestin expression in olfactory sustentacular cells implicated them with a new role as putative progenitor cells. In addition, she has published a comprehensive description of synaptogenesis in developing cochlea.

She was a founding member and is now President of AACSS, the Australasian Association of ChemoSensory Sciences, a society promoting research into the chemosenses, olfaction and taste. In this activity she is a key player in promoting research and lobbying for funding for research into the sensory sciences in Australia, and represents Australia to the international sister organisations, AChemsS, ECRO, and JASTS.

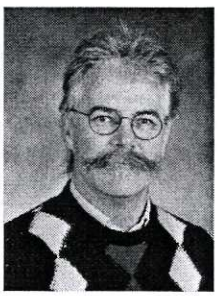
Her current research interests include olfactory neural stem cells; the role of trophic factors in olfactory development; olfactory neurogenic mechanisms; olfactory axonal outgrowth and synaptogenesis; nervous system development and plasticity; therapeutic modalities of neuroprotection; and cell-based therapies for neurological insult and degenerative conditions.

MULTIPOTENT STEM CELLS FROM ADULT HUMAN NOSE

Alan Mackay-Sim
Institute for Cell and Molecular Therapies
Griffith University
Queensland

Stem cells are cells that can divide and differentiate to give rise to many different types of cells and tissues. Embryonic stem cells give rise to all types of cells in the developing embryo and are said to be "pluripotent". Adult stem cells reside in tissues that undergo repair, normally giving rise to a limited range of cell types. They are said to have "restricted potency". In recent years it has been realised that some adult stem cells can do more than this, that they have "multipotency". For example, haematopoeitic stem cells that normally make blood cells can also give rise to neurons and cardiac muscle, and are in multiple clinical trials of transplantation after cardiac infarct. Other adult stem cells can be found in the brain, bone marrow mesenchyme, skin, and milk teeth. We are exploring the biology of stem cells found in the adult human olfactory mucosa. The sensory neurons of the olfactory epithelium are replaced throughout adult life. This may be an evolutionary defence against potential loss of smell brought about by nasal infections, including many pathogens that can enter the brain via the olfactory nerve. It is well known that the olfactory epithelium must contain progenitors that rise to the different cells of the olfactory epithelium, especially the sensory neurons. We have focussed on the question of whether there exists a true stem cell in the olfactory mucosa that can give rise to cell types found in other tissue, non-olfactory tissues. Our research shows that 1) cells from adult rat olfactory mucosa generate leukocytes when transplanted into bone-marrow irradiated hosts, 2) cells from adult mouse olfactory epithelium generate numerous cell types when transplanted into the chicken embryo, 3) cells grown from human olfactory mucosa are multipotent in vitro and in vivo. These results demonstrate the presence of a multipotent stem cell in the human olfactory mucosa. We are exploring the use of these adult stem cells for transplantation repair of the nervous system. They are also proving useful for studying the biology and genetics of several diseases by providing a "window" into the cells of the brain.

Biography



Professor Alan Mackay-Sim is known internationally for his research on the olfactory system. He has published more than 70 original research articles, reviews, and book chapters in olfaction, gustation, vision, and neural development. A graduate of Macquarie University, New South Wales, Professor Mackay-Sim is currently the Deputy Director of the Institute for Cell and Molecular Therapies at Griffith University. His research is concerned with how new neurons are formed in the adult olfactory epithelium. This work has led to new insights into schizophrenia and is also being used to explore ways to repair the injured nervous system in a Phase I clinical trial of autologous transplantation of olfactory ensheathing cells in human paraplegia. Professor Mackay-Sim has been awarded a Senior Research Fellow by the Garnett Passe and Rodney Williams Memorial Foundation and a French Government Scientific Fellowship. He is currently Professor at Griffith University's School of Biomolecular and Biomedical Science. In 2003 he was named Queenslander of the Year.

ADVANCES IN IMAGING IN OTOLARYNGOLOGY

Andy Whyte
Magnetic Resonance Imaging Center
Western Australia

Significant technological advances have occurred in all major branches of imaging – ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine.

Improved resolution of US probes allows spatial resolution of 1mm. Differentiation between normal and abnormal tissues is very high and similar efficacy to MRI in the Head and neck. Deep tissues and bone are not adequately imaged. US is very operator dependant and cost effective.

CT has been revolutionised by multi-detector technology. This allows extremely rapid volumetric scanning. Reconstructions, either 2D or 3D are of excellent quality and resolution of the order of 0.5mm is now routinely possible.

MRI remains much slower than CT and its major advantage is its high contrast resolution allowing maximal differentiation between normal and abnormal tissue. Spatial resolution of selected sequences now equates with CT; volumetric scanning of the labyrinth and vestibulocochlear nerves allows resolution of the order of 0.6mm.

Positron Emission Tomography (PET) has been a major advance in staging and evaluating for relapse of certain tumours, especially melanoma and lung cancer. The limits of detection for melanoma and other tumours are 3 and 7mm respectively, melanoma being more metabolically active and easier to detect. The role of PET in Head and Neck cancer is evolving. Its major role is in detecting recurrent disease in those patients difficult to access radiologically or clinically, eg. Advanced laryngeal cancer treated by radiotherapy. PET compares the metabolism (glucose utilisation) of tumours compared with normal tissue. It requires a cyclotron to produce a labelled glucose molecule ("radioactive sugar"). Access is very limited, the technique is expensive, only 1 scanner per state is eligible for a rebate and referral indications are strictly defined. Optimal results are produced by a combination PET-CT scanner allowing anatomical – metabolic correlation.

Picture archiving and communication systems (PACS) are necessary to optimally evaluate the vast amount of date produced by imaging systems, especially multi-detector CT. Only a small amount of the data is presented on X-Ray film and in an increasing number of public hospitals, film has ceased to exist. Rapid image transfer and ease of storage are other obvious benefits.

The application of these technologies is discussed with reference to a range of clinical indications.

Biography

Andy Whyte qualified in Dentistry with Honours (BDS.Hons) from University of Birmingham, England in 1975. After 3 years of training in Oral and Maxillofacial Surgery, he commenced a shortened course in Medicine in 1978 at the University of Wales. After qualifying in 1982 and completing an intern's year, he was Chief Resident in Oral and Maxilofacial surgery in UCSF, California. Andy then commenced training in Radiology in Wales in 1984, with appointmens as a Lecturer in Dental Radiology (FRCR & DDRRCR), and undertook a fellowship in Head and Neck Radiology at UCLA, California. His first Consultant appointment was at the Royal Adelaide Hospital in 1989, followed by a move to Flinders Medical Centre and Private practice in 1990.

In 1998, Andy moved to Perth as a partner in Perth Radiological Clinic and initially as a consultant at the Royal Perth Hospital. He is now based solely in private practice with an Honorary Consultant's appointment to the Department of Otolaryngology/Head and Neck injury at Sir Charles Gairdner Hospital. Andy has over 40 publications, and is the imaging editor for the Australasian Journal of Otolaryngology.

The Garnett Passe and Rodney Williams Memorial Foundation

Frontiers in Otorhinolaryngology 2004

Abstracts for Poster Presentations

Poster no. 1

TYMPANIC MEMBRANE STRUCTURE – A PRELUDE TO TISSUE ENGINEERING

KS Anandacoomaraswamy*, T Robertson, N Dutton, RH Eikelboom, MD Atlas
Lions Ear and Hearing Institute, and School of Surgery and Pathology, The University of Western Australia.

Aim: To undertake electron microscopy and immunohistochemical studies of the normal human tympanic membrane as a basis to develop a tissue-engineered tympanic membrane.
Background: The functional results of myringoplasty, using currently available graft materials, remains uncertain. A tissue-engineered tympanic membrane should theoretically improve outcomes. Successful tissue engineering of the human tympanic membrane requires an intimate understanding of the cytokeratin (CK) expression of the outer and inner layers, for identification of cells in cell culture, as well as the collagen components of the middle layer.
Method: Tympanic membrane structure was examined histologically using standard techniques of light and electron microscopy. CK expression of the outer and inner layers, was analysed by immunohistochemistry
Results: Histology confirmed the three-layer structure of the tympanic membrane. The middle collagenous layer consists of outer radial and inner circular fibres, with parabolic fibres observed between them. The outer epithelial layer consists of an outer keratinising stratum corneum with underlying stratum granulosum, stratum spinosum, and stratum basale layers. The thin inner mucosal layer consists of simple squamous or cuboidal cells. CK 5 and 10 are expressed in the outer layer, with positive staining of CK 7 and 8 in the inner layer.
Discussion/Conclusion: CK expression of keratinocytes from the outer layer, and mucosal cells from the inner layer, enables us to test cell growth on different scaffolds and in different environments. We are progressing on our work to determine the collagen composition of the middle layer. This knowledge is necessary for the development of an appropriate scaffold to support cell growth. There is good evidence to suggest that the middle layer provides the tension of the tympanic membrane and its loss results in a flaccid tympanic membrane, with impaired function.

Poster no. 2

VESTIBULAR-AFFERENT RESPONSES TO MECHANICAL STIMULATION AND DRUG APPLICATION IN THE ISOLATED LABYRINTH

Aaron J. Camp, Heung-Youp Lee, Robert J. Callister, Alan M. Brichta
School of Biomedical Sciences, Faculty of Health, University of Newcastle, Callaghan, NSW 2308 Australia.

We have recently developed an *in vitro* preparation of the mouse inner ear and recorded intra-axonal activity from attached anterior and horizontal vestibular primary afferents. Despite the trauma associated with surgical isolation from the skull, the peripheral vestibular apparatus retains the ability to convert or transduce mechanical stimuli into electrical afferent activity at a range of temperatures (23 to 34°C). We used a custom-made micropusher to deform the membranous ducts through openings in the bony labyrinth and studied afferent activity in response to sinusoidal indentations. We recorded from more than 350 vestibular afferents, in response to a broad stimulus-frequency range (0.01 - 10 Hz), and usually observed concomitant sinusoidal changes in discharge rates. The results were remarkably similar to those reported in whole-animal experiments, despite the use of artificial stimuli. We also observed activity in afferents from adjacently stimulated canals, suggesting that endolymphatic flow in one canal can affect another. Our *in vitro* preparation also allowed us to monitor afferent discharge in response to drug application. We studied a number of neuromodulators thought to influence transduction and synaptic transmission. Our results show that tetrodotoxin, a sodium channel blocker, abolishes afferent discharge within 60 s or less by acting directly on afferent axons. In contrast, CNQX a glutamate blocker takes up to 6 minutes to abolish afferent activity because it acts at the hair cell / primary afferent synapse. A second application of CNQX abolished afferent discharge much faster (< 60 s) and suggests the drug remains bound to receptors for some time. We also exposed the preparation to streptomycin, a known ototoxic agent and potent blocker of the mechanosensitive channels in hair cells. The relatively rapid (and fully reversible) effects (< 120 s) suggest that **acute** streptomycin exposure preferentially affects vestibular afferents rather than hair cells. In short, the isolated mouse labyrinth is a viable preparation for study of mammalian peripheral vestibular function in ways that have been impossible until now.

Supported by Garnett Passe and Rodney Williams Foundation, Hunter Medical Research Institute, National Health and Medical Research Council of Australia,

Poster no. 3

BACKGROUND INHIBITORY SYNAPTIC TRANSMISSION IN MOUSE MEDIAL VESTIBULAR NUCLEUS NEURONS BEFORE UNILATERAL LABYRINTHECTOMY

Aaron J. Camp, Brett A. Graham, Robert J. Callister, Alan M. Brichta
School of Biomedical Sciences, Faculty of Health, University of Newcastle, Callaghan, NSW, 2308, Australia

Damage to the peripheral vestibular organs or vestibular nerve transection (labyrinthectomy) results in immediate and severe postural and eye-movement disturbances. With time, these symptoms generally abate by a process called **vestibular compensation**. Although important, we know little about the specific contribution of inhibition to vestibular compensation. Therefore, as a first step, we have recorded miniature inhibitory post-synaptic currents (mIPSCs) in the two physiological classes (Type A and Type B) of medial vestibular nucleus (MVN) neurons prior to unilateral labyrinthectomy. All experiments were in accordance with the University of Newcastle Animal Care and Ethics Guidelines. We obtained transverse brainstem slices (300 μm) from mice overdosed with Ketamine (100 mg/kg, i.p.) and recorded background activity in MVN neurons using whole-cell patch-clamp techniques (CsCl-based internal solution, holding potential -70mV; bath temp. 23°C). Of the 74 MVN neurons recorded, 63 received inhibitory input: 36 of these (57%) received exclusively $GABA_A$ inputs; 8 (13%) received exclusively Glycine inputs; and 19 (30%) received Mixed (both types) mIPSCs. We next examined if inhibitory drive differed for Type A and Type B MVN neurons. Using a combination of voltage- and current-clamp recordings, our results indicate that Type A neurons (n=8), receive **only** $GABA_A$ inputs, while Type B neurons (n=20), receive $GABA_A$, Glycine, and Mixed inhibitory inputs. In addition, we also labelled a subset of physiologically characterised MVN neurons (n=34) with neurobiotin. Our preliminary results suggest that neither location nor morphology can be used to distinguish the two types of neurons and their inhibitory inputs. Taken together, these findings show that *before* unilateral labyrinthectomy: 1) both $GABA_A$ **and** Glycine contribute to inhibitory synaptic processing in MVN neurons, and: 2) that inhibition mediated by $GABA_A$ and Glycine **differs** in Type A and Type B MVN neurons. Our next step is to compare these results with those obtained in animals that have undergone vestibular compensation *after* unilateral labyrinthectomy.

Supported by the Garnett Passe & Rodney Williams Memorial Foundation, Hunter Medical Research Institute

Poster no. 5

NOVEL MARKERS FOR POOR PROGNOSIS IN HEAD AND NECK CANCER

David CHIN[1,4,5], Glen M. BOYLE[1], Rebecca M. WILLIAMS[3], Kaltin FERGUSON[1], Nirmala PANDEYA[2], Julie PEDLEY[1], Catherine M. CAMPBELL[3], David R THEILE[4], Peter G. PARSONS[1] and William B. COMAN[5]
[1]Melanoma Genomics Group and [2]Cancer and Population Studies Group, Queensland Institute of Medical Research, Herston, Brisbane, Queensland 4029 and Departments of [3]Pathology and [4]Plastic Surgery, and [5]Head and Neck Unit, University of Queensland, Princess Alexandra Hospital, Woollongabba, Brisbane, Queensland 4102, Australia

HNSCC is one of the most distressing human cancers, causing pain and affecting the basic survival functions of breathing and swallowing. Mortality rates have not changed despite recent advances in radiotherapy and surgical treatment. We have compared the expression of over 13,000 unique genes in seven cases of matched HNSCC and normal oral mucosa. Of the 1,260 genes that showed statistically significant differences in expression between normal and tumor tissue at the mRNA level, three top ranking of the top 5% were selected for further analysis by immunohistochemistry on paraffin sections, along with the tumor suppressor genes p16 and p53, in a total of 62 patients including 55 for whom greater than 4 year clinical data was available. Using univariate and multivariate survival analysis, we identified SPARC/osteonectin as a powerful independent prognostic marker for short disease-free interval (DFI) ($P < 0.002$) and poor overall survival (OS) ($P = 0.018$) of HNSCC patients. In combination with other ECM proteins found in our analysis, PAI-1 and uPA, the association with DFI and OS became even more significant, $P < 0.001$ each. This study represents the first instance of SPARC as an independent prognostic marker in HNSCC.

Poster no. 4

ALPHA-B CRYSTALLIN, A NEW INDEPENDENT MARKER FOR POOR PROGNOSIS IN HEAD AND NECK CANCER

David CHIN[1,4,5], Glen M. BOYLE[1], Rebecca M. WILLIAMS[3], Kaltin FERGUSON[1], Nirmala PANDEYA[2], Julie PEDLEY[1], Catherine M. CAMPBELL[3], David R THEILE[4], Peter G. PARSONS[1] and William B. COMAN[5]
[1]Melanoma Genomics Group and [2]Cancer and Population Studies Group, Queensland Institute of Medical Research, Herston, Brisbane, Queensland 4029 and Departments of [3]Pathology and [4]Plastic Surgery, and [5]Head and Neck Unit, University of Queensland, Princess Alexandra Hospital, Woollongabba, Brisbane, Queensland 4102, Australia

Gene expression profiling has provided many insights into tumor progression but translation to clinical practice has been limited. We have compared the expression of 13,000 unique genes in seven cases of matched head and neck cancer tumors and autologous normal oral mucosa. Alpha-B crystallin (CRYAB) was in the top fifty genes identified with statistically significant differences in expression between tumor and NOM at the mRNA level. This was confirmed at the protein level by immunohistochemistry on paraffin sections, in a total of 62 patients including 55 for whom greater than four year clinical data was available. Using univariate survival analysis, we identified lack of alpha-B crystallin staining as a powerful and independent prognostic marker for disease-free interval ($P < 0.001$) and overall survival ($P < 0.002$) of HNSCC patients. Notably, all thirteen patients whose tumors lacked alpha-B crystallin had no recurrences (100%, $P < 0.001$). This included five of the 35 node-positive patients, a group who would routinely be treated aggressively with neck dissection and radiotherapy. Nineteen of 27 node-negative patients, for whom it is difficult to decide whether aggressive treatment would be beneficial, stained positive for alpha-B crystallin with over a third (37%) having recurrences. We conclude that presence or absence expression of alpha-B crystallin is a powerful marker for prognosis and could be used routinely to improve the management of HNSCC patients.

Poster no. 6

UNIQUELY HUMAN GENE (SGM1) CONTROLS LARYNGEAL/VOCAL DEVELOPMENT

Clarke RA and Fang ZM
Human Molecular Genetics Unit, 3rd Floor Research and Education Building, St George Hospital, University of NSW, Kogarah NSW 2217, r.clarke@unsw.edu.au

The ability to speak is a uniquely human trait which has its origins in combined cognitive, neurological and structural processes. The structure of the larynx is a principal component of the necessary vocal development essential for speech while individuals with vocal defects have substantial difficulty acquiring expressive and/or receptive language. The biological and/or genetic basis of vocal defects have been difficult to determine, primarily due to the absence or complexity of inheritance patterns in such disorders. Previously we described a five generation family (KF2-01) with autosomal dominant inheritance of vocal /laryngeal defects in association with the Klippel-Feil syndrome. We have since identified a mutation within the SGM1 gene as the causative agent within this family.

SGM1 regulates development of the larynx within the embryo in concert with the wider developmental regulation of facial structures including the ears and mouth and the development of spinal vertebrae. The unique pattern of spinal anomalies in a number of Klippel-Feil families with SGM1 gene mutations implicates SGM1 in developmental patterning. SGM1 appears to regulate segmentation within the axial mesoderm during somitogenesis. The common origin of facial and laryngeal development within the developing branchial arches suggests that SGM1 pattering may also be involved here. The severity of vocal defects within the KF2-01 family correlated closely with the severity of spinal abnormalities. This suggested an SGM1 dose affect common to both deformities – further supported by the fact that one copy of the SGM1 gene has been totally inactivated within this family.

SGM1 offers an unprecedented opportunity to investigate the genetics of vocal development and control. Of added interest here is the fact that SGM1 appears to be a 'uniquely human' gene without any remotely related mouse orthologue. As such SGM1 will also help define important elements of what it means to be human.

Poster no. 7

PERSISTENT PNEUMOCOCCAL INFECTION IN CHILDREN WITH OTITIS MEDIA WITH EFFUSION: THE ROLE OF BACTERIAL BIOFILM AND INTRACELLULAR INFECTION

Coates H, Richmond P, Langlands J, Thornton R,
Princess Margaret Hospital for Children and University of Western Australia School of Paediatrics and Child Health, Keil T, Vijayasekaran S, Princess Margaret Hospital for Children, Perth Western Australia, Fillion P, Pathcentre, Sir Charles Gairdner Hospital, Perth, Western Australia

Background: In otitis media with effusion (OME) at least 40-60% of effusions are sterile, however metabolically active bacteria can be detected using polymerase chain reaction (PCR). Oral antibiotics have poor efficacy in the treatment of OME These observations may be explained by the presence of biofilm which is a strategy used universally by bacteria for survival and has been demonstrated in chronic human infections such as cystic fibrosis and endocarditis. Biofilm renders bacteria resistant to antibiotics and immune attack and has been demonstrated in animal models of OM.
Aims: The purpose of this study was to investigate the presence of biofilm in children with OME using electron microscopy (EM), bacterial culture and bacterial PCR
Methods: 2mm Biopsies of middle ear mucosa from children with OME undergoing insertion of ventilation tubes were examined using EM for evidence of bacterial biofilm. Middle-ear effusion fluid (MEF) was sent for standard culture and microscopy (M/C/S) and PCR for pneumococcal pneumolysin.
Results: To date we have collected 16 mucosal samples and 15 samples of MEF from children with OME. MEF culture grew Haemophilus influenzae in 3 of the 15 samples, mixed Strep pyogens and Staph aureus in 1 but pneumocaccus and Moraxella have not been isolated. Of the remaining 11 samples, 3 (33%) were positive for pneumolysin PCR; and 4 of these had cocci bacterial identified in epithelial cells or epithelial stroma on EM. We have been unable to demonstrate the presence of pneumococcal biofilm in these samples. This may relate to the small amount of mucosa biopsied or biopsy and/or processing techniques, which are under review.
Conclusions: This provides further indirect evidence for a role for pneumococcal infection in the pathogenesis of OME. Whether this is due to the presence of pneumococcal biofilm or due to sequestration of pneumococci in epithelial cells remains to be elucidated.

Poster no. 8

SURVIVAL AND MIGRATION OF PARTIALLY DIFFERENTIATED STEM CELLS IN THE DEAFENED GUINEA PIG COCHLEA

B. Coleman[1], J. Hardman[2], J. Crook[3], M. de Silva[4], S. Epp[2], A. Coco[2], and R. Shepherd[1,2]
[1]Department of Otolaryngology, University of Melbourne, [2]Bionic Ear Institute, Melbourne, [3]ES Cell International, Melbourne, [4]Murdoch Institute, University of Melbourne.

Spiral ganglion neurons (SGNs) degenerate following a sensorineural hearing loss due to lack of trophic support normally received from hair cells. Although recent experimentation has shown that SGNs can be maintained by constant infusion of exogenous neurotrophins, this survival effect is lost immediately following the termination of treatment [1]. Stem cell (SC) transplantation therapy is emerging as a potential strategy for inner ear rehabilitation as differentiated SCs may provide a source of functional neurons to the damaged cochlea. An increase in SGNs is likely to result in improved efficacy for cochlear implants (CIs). In this study, we examined the survival and migration of partially differentiated SCs following a xenograft transplant into the scala tympani of deafened adult guinea pigs. SCs were differentiated into primitive neuronal tissue prior to transplantation and detected via direct microscopic visualisation of endogenous green fluorescent protein (GFP) 1, 2 and 4 weeks post-transplantation. SCs were observed in the scala tympani and scala vestibuli and had migrated through all turns of the cochlea at each time point. Conversely, SCs were not detected in the scala media where Reissner's membrane was intact. Transplanted SCs adopted an astrocyte-like morphology which they did not display *in vitro*, however small numbers of these cells were positive for the neuronal marker neurofilament (NF-L) after 4 weeks *in vivo*. Importantly, no fibrous tissue response was observed as a result of transplantation surgery in any of the experimental animals. In addition, small numbers of SCs appeared to have migrated into parts of the osseous spiral lamina and the modiolus. Results illustrate that SCs have the capacity to survive, migrate and differentiate within the cochlea for up to 4 weeks without causing an inflammatory reaction. These techniques hold promise for the application of cell-based therapies in combination with CIs. [1]Gillespie et al. *J. Neurosci. Res.* **71**:785-790 (2003).

This work was funded by the University of Melbourne and the NIDCD (N01-DC-0-2109 and N-01-DC-3-1005).

Poster no. 9

THE EFFECTS OF CHILDHOOD OTITIS MEDIA ON THE ACOUSTIC REFLEX THRESHOLD AT AGE 15

D Welch, PJD Dawes. The Dunedin Multidisciplinary Health and Development Study, University of Otago, Dunedin, New Zealand

Aim: To investigate the effect of audiometric threshold and tympanic membrane condition upon the acoustic reflex threshold (ART) at age 15 years. **Background**: Previous research has shown elevated adulthood ART to be an effect of childhood otitis media [1]. Audiometric threshold in the ear to which stimulation was delivered, and abnormality of the tympanic membrane in the ear from which ART was measured were found to be the two most important determinant variables. **Method**: The Dunedin Multidisciplinary Health and Development Study is a large scale longitudinal study utilising a birth cohort of 1037 people born in Dunedin from April 1972 to March 1973. Measures were taken of the degree of otitis media (OM) experienced at the ages 5, 7, and 9, childhood audiometric thresholds at age 11, measures of ART at 15, and detailed otological description of the tympanic membrane at age 15. Measures were taken at all five ages from 631 children. The degree of OM experienced between these years was previously determined, based upon a set of persistence and severity criteria[2]. ANOVA was used to investigate the effects of both audiometric threshold and OM on ART measured at each ear, and with both ipsilateral and contralateral stimulation. **Results:**The main findings were: 1) Raised ART was measured in those who had experienced most OM during childhood. This supports the earlier findings[1], and extends them in that it may be said that only those who experienced more persistent childhood OM have an elevated ART. 2) ART is predicted by a history of childhood OM in a way that is partly mediated by the effect of stimulus ear audiometric threshold. 3) ART is predicted by extent of childhood OM, mediated by the effects of probe ear TM status. **Conclusion**: Our findings generally support hypotheses based upon earlier work[1]. The techniques used in the two pieces of research differed markedly. The earlier work was based on careful ART measurement in a small sample, with retrospective measures of childhood experience of OM. The present work was based on a large sample, with standard protocols for ART measurement, and with prospective measures of childhood experience of OM. The strong agreement in findings of these disparate research methods greatly supports the conclusions drawn.

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Poster no. 10

SALIVARY COMPONENTS PROMOTING ADHERENCE OF *CANDIDA ALBICANS* TO VOICE PROSTHESIS SILICONE RUBBER.

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Background: Interactions between Candida albicans, saliva and saliva-coated oral surfaces are initial events in the colonisation of the oral cavity by this commensal yeast, which also adheres to voice prostheses. The consequent biofilm formation impairs valve function, necessitating frequent prosthesis replacement. Current antifungal therapies are either toxic, or carry long-term risks of inducing drug resistance, and have been shown to be ineffective in preventing prosthethetic device failure. New therapies are required.

Aims: Our hypothesis is that interference with the adherence of C. albicans to silicone rubber may prolong the in situ lifetime of voice prostheses.

Methods and Results: In order to investigate the role of saliva components in the adherence of C. albicans to voice prostheses, we have developed assays which measure adherence of radiolabelled yeast cells to saliva coated silicone rubber discs and to salivary proteins separated by polyacrylamide gel electrophoresis (PAGE) and electroblotted onto nitrocellulose membranes. Pooled human whole saliva promoted (by >150%) adherence of C. albicans to silicone rubber. In addition, a number of salivary polypeptides were shown by PAGE analysis to be selectively bound from whole saliva to silicone. When released from the silicone, two were shown to bind radiolabelled C. albicans cells, as detected by autoradiography. One polypeptide was identified by N-terminal sequencing as Parotid Secretory Protein (Genbank Accession # AAL28113). We are currently investigating the prevalence of these proteins in patient saliva.

Conclusions: We have identified salivary proteins that mediate adherence of C. albicans to voice prosthesis silicone rubber. Such adherence interactions may provide targets for new approaches to prosthesis design and patient treatment, that would decrease the formation of Candida biofilms on the valves, and the frequency of prosthesis replacement. This study was supported by a University of Otago Research Grant (#0020030854).

Poster no. 11

UNILATERAL PROFOUND HEARING LOSS AND QUALITY OF LIFE AFTER CEREBELLOPONTINE ANGLE SURGERY

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Objective: Assessment of patient's quality of life after cerebellopontine angle surgery and in particular quality of life related to unilateral profound hearing loss.
Study design and setting: Cross-sectional in a tertiary referral centre. Quality of life of 51 post-operative patients was assessed using the Glasgow Benefit Inventory (GBI). 30 patients with unilateral profound hearing loss who had undergone the translabyrinthine approach completed a subsequent quality of life questionnaire on speech discrimination and sound localisation.
Results: 94% of respondents to the second survey reported difficulties with speech discrimination and 97% with sound localisation. The general health and overall GBI indices correlated significantly ($p<0.01$) with a number of speech and localisation difficulties.
Conclusion: Unilateral profound hearing loss may be a significant factor in a change in quality of life after cerebellopontine angle surgery.
Significance: Rehabilitation devices that improve discrimination and localisation, and hearing preservation surgery, if indicated, should be considered for these patients.

Poster no. 12

DIFFERENTIAL GENE EXPRESSION BETWEEN NASOPHARYNGEAL CARCINOMA AND NORMAL NASOPHARYNGEAL MUCOSA

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The development of nasopharyngeal carcinoma is associated with a number of genetic changes that result in the activation of oncogene and inactivation of tumour-suppressor genes. Using the recently developed technology of cDNA microarrays we determined differential gene expression between matched nasopharyngeal tumour and adjacent normal nasopharyngeal mucosa in 3 patients using OCI microarray chips that screen for 18,107 gene sequences. Gene profiles when then compared between the three patients to identify genes up- or down-regulated in common to at least 2 of the three patients. Overexpression of glutathione *S*-transferase and osteonectin, and reduced expression of T-cadherin was found. Confirmation of protein expression for each of these genes was performed with immunohistochemistry. Technologies such as microarray analysis are contributing to the exponential understanding of the molecular biological changes in nasopharyngeal carcinoma.

Poster no. 13

NEUROTROPHIN SURVIVAL EFFECTS ON AUDITORY NEURONS IN VIVO

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Neurotrophic factors, in particular the neurotrophins brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) are well known to be important for the development and maintenance of the auditory system[1] and have also been reported to act as survival factors for auditory neurons in animal models of deafness. Indeed, numerous studies have demonstrated that intracochlear application of neurotrophins shortly following deafening can prevent auditory neuron degeneration[2-4]. Following on from these findings, we have investigated two aspects of the time-course of neurotrophin-induced auditory neuron survival.

Firstly, we tested the longevity of the survival effects of BDNF on auditory neurons in deaf guinea pigs; specifically we aimed to determine if the survival effects of BDNF are maintained beyond the period of treatment, or if sustained delivery is required. Results from this study indicated that while BDNF prevents auditory neuron degeneration during the treatment period, cessation of the trophic support leads to a rapid loss of survival effects. These findings suggest ongoing neurotrophin treatment may be required for maintained auditory neuron survival.

Secondly, we examined the effects of delayed neurotrophin treatment on auditory neuron survival following deafness. Results from this study demonstrated that each of the members of the neurotrophin family – BDNF, NT-3, neurotrophin 4/5 (NT-4/5) and nerve growth factor (NGF) – can rescue auditory neurons from degeneration after a two-week period of deafness. These findings show that neurotrophins can be effective survival agents even when the degenerative processes are well underway.

The results of these studies provide further support to the theory that neurotrophic factors may ultimately be able to be used as therapeutic agents for the benefit of the hearing impaired community, but suggest that ongoing treatment, or combined use of alternative therapies, may be necessary.

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Poster no. 14

SURVIVAL OF STEM CELLS FOLLOWING XENOGRAFT IMPLANTATION INTO THE ADULT GUINEA PIG COCHLEA

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The low regenerative capacity of the hair cells of the mammalian inner ear is a major obstacle for functional recovery following trauma to the auditory system. A potential treatment is to regenerate or replace these cells by transplantation of stem cells. This treatment may stimulate development of existing cells into hair cells or the transplanted cells may integrate to replace lost or damaged cells. To test the feasibility of this approach undifferentiated and partially differentiated mouse embryonic stem (ES) cells, expressing enhanced green fluorescent protein (EGFP) were delivered into the scala media of the normal and deafened adult guinea pig cochlea. Transplanted embryonic stem cells survived in the cochlea for a post-operative period ranging from 2 to 4 weeks, evidenced by histology and detection of EGFP. ES cells were discovered near the spiral ligament and stria vascularis and in the endolymph fluid of the scala media cavity. In one case ES cells were observed close to the damaged organ of Corti structure, which may indicate the potential of these cells to migrate to sites of trauma although further investigation is required. Transplanted cells were also found in the scala tympani cavity and many of these cells localized close to the basilar membrane below the organ of Corti. In some cases ES cells were also found in the scala vestibuli. There was no evidence of immunological rejection of the mouse ES cells in the scala media cavity and only minor indications in other areas of the cochlea. The surgical procedure appeared to be atraumatic as the integrity of the cochlear structure was preserved. These results indicate not only the survival of mouse ES cells in the adult guinea pig inner ear for up to 4 weeks but also the ability of these cells to localise close to endogenous tissue after transplantation. The surviving stem cells might have the potential to replace or regenerate hair cells damaged by injury to the auditory system.

Poster no. 15

MUSIC PERCEPTION BY COCHLEAR IMPLANTEES: DOES FILTERING AND/OR COMPRESSION AFFECT SOUND QUALITY?

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Signal filtering and compression adversely affects music sound quality for normally hearing listeners. However, this has never been investigated in cochlear implant (CI) users, despite inherent filtering and compression in CI processing, e.g. CI microphones and accessory cables filter signals at +6 and +12 dB/oct respectively. In this study, the Judgment of Sound Quality questionnaire was used to assess the effects of signal manipulation in 13 adult Nucleus CI 24 users. The manipulations investigated were: 1) filtering, at –6, +6, +12 dB/oct; 2) compression at 2:1, 4:1 and 8:1, and expansion at 1.5:1; and 3) compression at 2:1 with additional filtering as above. Signal expansion, and the application of the –6 dB/oct filter, with and without compression were rated as significantly poorer than normal. None of the other manipulations were consistently rated as significantly different from normal. This indicates that, unlike in normal hearing, compression does not detract from music quality, and that the filtering inherent in CI microphones and accessory cables does not adversely affect sound quality in CI users.

Poster no. 16

PREVENTION OF COCHLEAR INFECTION AND MENINGITIS POST COCHLEAR IMPLANTATION

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Background: An increased risk of developing bacterial meningitis amongst cochlear implant recipients has recently become evident. We set out to illustrate and delineate the pathogenesis, routes of bacterial spread, in the early phases of bacterial invasion in to the implanted cochlea. As the round window membrane can act as bacterial conduit into scala tympani, we examined the effects of grafting it in order to prevent bacterial invasion.

Methods: Utilising the current implantation techniques, a silicone only Nucleus® Contour™ electrode was implanted in an animal model. Inoculation of *Streptococcus pneumoniae* into the middle ear was carried out a month post-implantation. Twenty-four hours post-inoculation, blood, cerebro-spinal fluid (CSF), middle ear fluid, and temporal bones were extracted for analysis.

Results: All subjects had purulent otitis media. All blood cultures were negative except one, and no bacteria were demonstrated in the CSF. Histopathology revealed a fibroepithelial peri-implant seal. There was tracking of bacteria and polymorphs between the seal and the implant. Occasional bacterial spread was observed outside the seal into ST in the absence of suppurative labyrinthitis.

Lymphovascular seeding of bacteria through the seal and the round window niche was demonstrated. Grafting thickened the round window membrane up to 23 times its normal size. Bacteria were observed in both grafted and ungrafted round window membranes, however grafting increased the distance between the infected middle inner ear and the scala tympani.

Conclusions: The circum-implant fibroepithelial seal acts as a dynamic biological barrier that protects the cochlea in the early phases of bacterial acute otitis media. The seal does not always prevent the spread of bacteria into the intracochlear portion of the electrode, but like the middle ear mucosa, it could be effective in resisting bacterial invasion. Grafting the round window membrane can provide a mechanical barrier to bacterial invasion into the cochlea in the early phases of bacterial AOM.

Poster no. 17

HIGH FREQUENCY (1000 Hz) TYMPANOMETRY FINDINGS IN NEWBORN VERSUS 3-WEEK-OLD INFANTS

Dr. Jack KU, Dr. Joseph KEI, and a panel of ENT surgeons in Queensland, Australia. Hearing Research Center, University of Queensland and Queensland Health.

It is recognized that mild-moderate hearing impairment in young infants prior to 6 months of age can cause speech and language deficits. Current screening tests are inadequate in measuring middle ear function, especially in the detection of a mild conductive hearing loss. The literature has shown promise in the use of a higher frequency (e.g. 1000 Hz) tympanometry but past studies were small and none extensively document the characteristics of the tympanograms of 3-week-old babies correlated with postnatal maturational changes of the middle ear system. The present study aimed to describe the characteristics of the conventional (226Hz) tympanometry and 1 kHz tympanometry of newborns and 3- week-old infants, in relation to the developmental changes in their middle ears.

Transient evoked otoacoustic emission (TEOAE) and tympanometry (226 Hz and 1 kHz) testing were performed using a Madsen Capella OAE / middle ear analyzer on 151 (69 male, 82 female) healthy full-term neonates (mean age of 1.57 days) and repeated on 118 (55 male, 63 female) 3-week-old babies (mean age of 22.46 days). The TEOAE outcomes were compared against the tympanometric findings. The TEOAE and tympanometric morphology obtained from the two age groups was compared.

An estimate of the performance of the 1 kHz tympanometric test using TEOAE as a surrogate – gold standard revealed relatively high specificity (82.0%) but a low sensitivity (39.5%) of the test for newborn babies. However, its performance improved to 90.1 % (specificity) and 75.0% (sensitivity) in 3-week-old babies.

The authors concluded from the analysis of the range of differential 1kHz tympanometric morphology in the 2 subject groups, that 1kHz tympanometry may be a suitable test for assessing the middle ear function of newborns and especially 3-week-old babies. It is also found the maturation of the auditory system of the neonates has resulted in statistically significantly different tympanometric results between the two subject groups.

Poster no. 18

DEREGULATED CYCLIN D1 EXPRESSION IS ASSOCIATED WITH DECREASED EFFICACY OF THE SELECTIVE EGFR TYROSINE KINASE INHIBITOR ZD1839 IN HEAD AND NECK SQUAMOUS CELL CARCINOMA CELL LINES.

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Purpose: Despite promising initial results, recent phase III trials of the selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor ZD1839 in advanced head and neck squamous cell carcinoma (HNSCC) have been equivocal. Cyclin D1, an EGFR target gene, is frequently overexpressed in HNSCC, has been implicated in its pathogenesis and is strongly associated with poor prognostic outcome in this disease. We therefore examined the relationship between deregulated cyclin D1 expression and sensitivity to ZD1839 to determine whether this frequently occurring oncogenic change affected the cellular response to ZD1839.
Experimental design: A panel of six EGFR-overexpressing HNSCC cell lines was used to correlate CCND1 gene copy number, cyclin D1 expression and response to ZD1839. The effect of constitutive overexpression of cyclin D1 was assessed by establishing stably transfected clonal SCC-9 cell lines.
Results: There was a significant correlation between ZD1839 sensitivity and CCND1 gene amplification but not endogenous cyclin D1 expression. Despite inhibition of EGFR signaling, cyclin D1-overexpressing clones continued to proliferate and maintained their S phase fraction when treated with ZD1839, whereas empty vector control clones and the parental SCC 9 cells were profoundly inhibited and displayed marked reductions in S phase. The resistance of cyclin D1-overexpressing clones and cyclin D1-amplified cell lines was associated with maintenance of cyclin D1 expression.
Conclusions: These data suggest that deregulated cyclin D1 overexpression may be associated with resistance of HNSCC to EGFR inhibitors. Therefore, the role of cyclin D1 as a marker of therapeutic response and its utility as a prognostic marker in HNSCC warrant further analysis.

Poster no. 19

EFFECTS OF ZD1839 ("IRESSA") UPON CELL CYCLE PROTEINS IN HEAD & NECK SQUAMOUS CELL CARCINOMA (HNSCC) & HNSCC CELL LINES

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Purpose: Up to 80% of head and neck squamous cell carcinomas (HNSCC) overexpress epidermal growth factor receptor (EGFR). The critical role of EGFR in cancer through cell proliferation, apoptosis, angiogenesis and metastatic spread, has led to the development of molecular therapies such as ZD1839 ("Iressa") – a selective EGFR-tyrosine kinase inhibitor. ZD1839 clinical trials in advanced HNSCC have shown benefit in patient survival, although, the mechanistic effect of on cell cycle regulation and molecular pathways remain to be shown.
Experimental Design: Immunohistochemical analysis of EGFR and cell cycle regulators such as $p16^{INK4A}$, cyclin D1, pRb, E2F-1, $p14^{ARF}$ and p53 were examined in a cohort of 145 patients with SCC of the anterior tongue. 6 HNSCC cell lines with varied EGFR expression, were treated with ZD1839 and protein expression of these molecules was assessed. The relationship between *in vivo* expression of these cell cycle proteins, *in vitro* protein expression and disease outcome was examined.
Results: Improved disease outcome was associated with overexpression of EGFR (P=0.020), $p16^{INK4A}$ (P=0.011) and E2F-1 (P=0.027), and reduced expression of cyclin D1 (P=0.010), pRb (P=0.06) and $p14^{ARF}$ (P=0.025) on Kaplan Meier analysis. p53 expression was not significantly associated with disease outcome. ZD1839 treatment of the HNSCC cell lines resulted in increased EGFR, $p16^{INK4A}$ and E2F-1 expression, whilst decreases in cyclin D1, pRb and $p14^{ARF}$ protein expression were observed. P53 expression remained unchanged from the control group.
Conclusions: ZD1839 treatment in HNSCC cell lines results in a cell cycle protein profile consistent with improved disease free and overall survival in HNSCC *in vivo*.

Poster no. 20

$p14^{ARF}$ PROTEIN EXPRESSION IS A PREDICTOR OF PROGNOSIS IN SCC OF THE ANTERIOR TONGUE

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Purpose: The *INK4A-ARF* locus at chromosome 9p21 is frequently altered in head and neck squamous cell carcinoma (SCC) and encodes two distinct tumour suppressors, $p16^{INK4A}$ and $p14^{ARF}$. This study addressed the role of $p14^{ARF}$, which has not previously been elucidated.
Experimental Design: $p14^{ARF}$ protein expression was assessed by immunohistochemistry in a cohort of 145 patients with SCC of the anterior tongue. Using univariate and multivariate Cox's proportional hazards models, the outcomes examined were time to disease recurrence or death, with or without clinicopathological covariates including: nodal status, disease stage, treatment status, and molecular markers with known functional or genetic relationships with $p14^{ARF}$ ($p16^{INK4A}$, p53, pRb, $p21^{CIP1/WAF1}$ and E2F-1).
Results: On multivariate analysis, $p14^{ARF}$ positivity (nucleolar $p14^{ARF}$ staining and/or nuclear $p14^{ARF}$ staining in ≥30% of tumour cells) was an independent predictor of improved disease free survival (DFS; hazard ratio [HR]: 2.9; P= 0.003) and overall survival (OS; HR: 3.4; P= 0.003). This was further enhanced when $p14^{ARF}$ positivity was co-segregated with positive (>1%) $p16^{INK4A}$ staining (DFS; HR: 4.6; P< 0.0001; OS; HR: 4.3; P= 0.0004). Patients with $p14^{ARF}$ negativity combined with high p53 staining (>50%) had the poorest outcome (DFS; HR: 4.1 P= 0.0002; OS; HR: 5.2 P< 0.0001) of any patient subgroup analyzed.
Conclusions: These data demonstrate that in patients with SCC of the tongue, overexpression of $p14^{ARF}$ protein predicts improved DFS and OS independent of established prognostic markers. Moreover, biological relationships and involvement of $p14^{ARF}$ in tumour inhibitory pathways, containing either p53 or $p16^{INK4A}$, were verified in subgroup analyses of patients with variable relative expression of these proteins.

Poster no. 21

A CLINICAL TEST OF SMELL FOR SCHOOL-AGE CHILDREN

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Currently there is no standard test that ENT clinicians can use for the assessment of smell in children. Although tests have been developed for adults eg the University of Pennsylvania Smell Identification Test and the German 'Sniffin Sticks' test, their cognitive requirements and duration make them unsuitable for use with children under about 10 yr. Diagnosis of smell dysfunction in children, therefore, is rare, whilst the health and social consequences are largely unknown. Accordingly, the present project aims to develop a test of smell for children aged 5 yr and above, based on smell identification that could be used by ENT clinicians and as part of the health screening programme in schools.

Stage 1 of the 3-stage programme has been completed with the assessment of 21 common odours representing 21 categories of smell by 298 5-9 yr olds and 47 adults. The aim was to determine the odours that children aged 5 yr and above could be expected to identify from their daily experiences. The test required the participants to identify each odorant, sniffed from a bottle, from sets of 4 photographs or words. All tests were conducted at schools on an individual basis by a trained assessor. The data described here are from the sets of photographs since the responses were best from this information mode. The results indicated that 90% (the criterion level for an odorant to be considered suitable for inclusion in a general test of smell) of 5, 6, 7, 8 & 9 yr olds and adults, correctly identified 10, 10, 12, 14, 15 & 17 of the 21 odorants, respectively. Odorants poorly identified by the adults were considered to be inadequate representatives of odour types. In contrast, mis-identification of the others by the children was mostly due to some similarity they found, albeit small, between the target odour and one of the other 3 odours in the sets of 4, or the odour was unfamiliar to the 5-7 yr olds eg mothballs. In addition, there was evidence that the errors made in some instances by some of the 5-6 yr olds were due to the cognitive demands of the 4-choice task.

In Stage 2 (July-November 2004), the number of odour categories will be reduced to 17 representing the best identified odours by the youngest children, the task will be simplified to a 3-choice set of photographs, and the photograph(s) inducing most of the errors in the original sets of 4 will be removed. It is anticipated these changes

Poster no. 22

OBJECTIVE ASSESSMENT OF OLFACTORY DYSFUNCTION

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Olfactory dysfunction is difficult to assess in the clinic and may be overlooked as an important moderator of quality of life. Establishing the extent of olfactory dysfunction may also be important in medicolegal cases. Olfactory abilities typically change with age, with most of the population losing olfactory function gradually after the age of 50. This makes it difficult to ascribe loss of olfaction to any particular life event - illness or accident. Self-assessments of olfactory abilities are often unreliable. As with vision and audition, olfactory assessment requires quantitative, objective tests that have been validated in the normal population. We developed Australian norms for age and sex for one of these quantitative tests, the "Sniffin' Sticks", based on almost 1000 persons aged 10 - 90. Using statistical criteria against this general population, we identified test scores that classify people into "normosmic, "hyposmic" and "anosmic". These functional classifications were tested against a population of people with Parkinson's disease. As predicted, the large majority of these patients were classified as anosmic or severely hyposmic (81%), demonstrating the utility of these classification scores. Olfactory function is also quantitatively assessed using chemosensory evoked potentials. These are scalp-recorded, event-related potentials occurring after a chemosensory stimulus. It is not often realised that most odorants stimulate the trigeminal nerve, giving sensations of odour strength and pungency. In anosmia, trigeminal function may be the only means of "smelling" which both patients and clinicians can mistake for olfaction. Chemosensory evoked potential recording is the only objective method to distinguish trigeminal nerve activity from olfactory nerve function and the only method to assign definitively a classification of "anosmia" in medicolegal cases. We are investigating cases of parosmia, where most odours smell bad. Preliminary evidence suggests that in these cases olfactory nerve function is reduced but trigeminal function is increased. Trigeminal function does not appear to be increased in total anosmia after head injury, suggesting a role for the trigeminal nerve in parosmia.

Poster no. 23

NERVE GROWTH FACTORS IMPROVE THE FUNCTION OF THE AUDITORY NERVE AFTER HEARING LOSS: IMPLICATIONS FOR COCHLEAR IMPLANTATION

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Aims: Successful cochlear implantation relies upon effective stimulation of the auditory nerve, but sensorineural deafness is associated with a decrease in the number of surviving auditory neurons and a reduction in their functional status. This may reduce the efficacy of the cochlear implant. Nerve growth factors (neurotrophins) have recently been shown to prevent auditory neurons from dying after a sensorineural hearing loss. We investigate whether neurotrophins also improve neuronal function.
Methods: Recordings were made from individual auditory neurons of adult guinea-pigs with either normal hearing, or deafened 1 or 6 months prior by a single dose of kanamycin, 400 mg/kg s.c. and frusemide, 100 mg/kg i.v. The neurotrophin, brain derived neurotrophic factor (BDNF) was delivered to the cochlea of another group of animals for 1 month, commencing 1 week after deafening. All experimental procedures were performed under a general anaesthesia of ketamine and xylazine, and were approved by the Animal Research and Ethics Committee of the RVEEH. For the electrophysiological recordings animals were implanted with a custom cochlear prosthesis that delivered biphasic, charge balanced, monopolar, 50 μs/phase electrical pulses. 100 ms duration trains of electrical pulses were delivered at rates of 20 and 200 pulses/s.
Results: There was a significant decrease in the latency of action potentials following deafness, which is indicative of a degeneration of the distal (peripheral) axon of these neurons after the hair cells are lost following deafness. More stimulus current was required to drive the neurons from deafened animals to their maximum firing levels. In BDNF treated animals, the latency did not decrease, and the threshold current required to excite the neuron decreased below normal levels. We conclude that there was less axonal degeneration after BDNF treatment, and that the treated neurons had become more excitable than normal. This would reduce the power consumption required for operation of the cochlear implant.

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Poster no. 24

PRESYNAPTIC PLASTICITY AT TWO GIANT AUDITORY SYNAPSES IN NORMAL AND DEAF MICE

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Large calyceal synapses are often regarded as simple relay points, built for high-fidelity and high-frequency synaptic transmission and a minimal requirement for synaptic plasticity, but this view is oversimplified. Calyceal synapses can exhibit dramatic short-term synaptic depression in response to physiological stimuli, and surprising activity-dependent developmental plasticity. Here we compare basal synaptic transmission and activity-dependent plasticity at two stereotypical calyceal synapses in the auditory pathway, the endbulb and the calyx of Held. Basal synaptic transmission was more powerful at the calyx than the endbulb synapse: the amplitude of evoked AMPA receptor-mediated excitatory postsynaptic currents (eEPSCs) was significantly greater at the calyx, as were the release probability, and the number of release sites. The quantal amplitude was smaller at the calyx, consistent with the smaller amplitude of spontaneous miniature EPSCs at this synapse. High-frequency trains of stimuli revealed that the calyx had a larger readily releasable pool of vesicles (RRP), less tetanic depression and less asynchronous transmitter release. Activity-dependent synaptic plasticity was assessed in congenitally deaf mutant mice (*dn/dn*). Previously we showed that a lack of synaptic activity in deaf mice increases synaptic strength at the endbulb of Held via presynaptic mechanisms. In contrast, we have now found that lack of activity does not affect synaptic transmission at the calyx synapse, as eEPSC amplitude, release probability, number of release sites, size of RRP, tetanic depression and asynchronous release were unchanged compared to normal mice. Synaptic transmission at the calyx synapse is more powerful and has less capacity for developmental plasticity compared to the endbulb synapse.

Poster no. 25

UNIQUE FUNCTIONAL PHENOTYPES OF NASAL POLYP LYMPHOCYTES IN EOSINOPHILIC MUCIN CHRONIC RHINOSINUSITIS (EMCRS)

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Background: EMCRS, a variant of chronic rhinosinusitis (CRS) is defined by tenacious eosinophilic mucin in the sinuses. Eosinophilis and lymphocytes characterize the mucosal cell infiltrate in EMCRS and other forms of polypoid CRS. It is unclear why EMCRS is associated with abundant eosinophilic mucin, extensive polyposis with tissue destruction and an aggressive clinical course. Fungi are often detected in the mucin of EMCRS patients, yet their pathogenic role is uncertain. We hypothesize that an immune pathogenesis is involved and the mucosal immune system is responding more aggressively in EMCRS compared with other forms of CRS. **Objective:** To compare and relate the phenotype, function and fungal-specific responses of lymphocyte populations from nasal polyps and paired peripheral blood samples in EMCRS patients. **Method:** Lymphocytes in polyp and blood from EMCRS (n=12) and CRS (n=6) patients were studied using multi-parameter flow cytometry. Fungal-specific peripheral blood cell proliferation in EMCRS (n=13) was assessed with [^{3}H]-thymidine assays. Mitotic activity was determined in cells labelled with carboxyfluorescein succinimidyl ester (CFSE). Results were compared with healthy volunteers (n=7) and disease-controls, CRS (n=11) and fungal allergic patients without sinusitis (n=14). **Results:** More T cells were present in EMCRS polyps compared with CRS ($p=0.01$). CD8+ cells were sequestered into EMCRS polyps in significantly higher levels (>2.4 fold) than in matched peripheral blood samples ($p<0.0001$) compared with CRS (1.2 fold, $p=0.03$). CD4+ T cell population was reduced in EMCRS polyps than in peripheral blood compared with CRS. CD45RA- and CD27- phenotype was predominant in CD8+ cells in EMCRS and in CD4+ cells in CRS polyps. Increased T cell proliferation to fungi was present in EMCRS compared with CRS patients ($p=0.03$). Fungal-specific T cell responses are currently being examined. **Conclusion:** EMCRS polyp lymphocytes were characterized by CD8+ memory T cells with an effector phenotype. Profound differences in the functional phenotypes of lymphocytes in eosinophilic polyps from EMCRS and CRS suggest distinct pathogenic mechanisms.

Poster no. 26

THE NITINOL STAPES PISTON: THE END OF MANUAL CRIMPING?

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Objective: The evolution of stapes surgery has encountered the development of several surgical techniques and stapes prostheses. There is increasing evidence that inappropriate crimping of the stapes piston is responsible for the significant variations of postoperative air-bone gap closures and postoperative recurrences of conductive hearing loss. To eliminate the influence of manual crimping on postoperative outcomes, the selfcrimping, shape memory nickel-titanium alloy Nitinol stapes piston was used. We investigated the effects of the selfcrimping Nitinol piston on the postoperative air bone gap variability and the postoperative short-term hearing results. **Study design:** Prospective preliminary study of 9 patients with otosclerosis undergoing reversed stapedotomy using the the Nitinol stapes piston.**Setting**: Tertiary care referral center. **Main Outcome Measures:** Pre-and postoperative puretone average hearing levels were assessed and the variations of the postoperative residual air bone gap calculated. These data were statistically compared with the results of our titanium stapes piston database. **Results**: The preoperative hearing levels were similar in both groups, The mean postoperative air bone gap closure was similar in the both groups, the variations of postoperative air bone gap closure, however, were significantly smaller in the Nitinol piston group. The postoperative short-term stability of air bone gap closure was similar in both groups. **Conclusion**: The nickel-titanium shape memory stapes piston eliminates the drawbacks of manual crimping in otosclerosis surgery, thus simplifying the surgical procedure. The short-term results show reliable, efficient and consistent air bone gap closure after stapedotomy.

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Poster no. 27

EFFECT OF THE MODIFIED ENDOSCOPIC LOTHROP PROCEDURE ON FRONTAL SINUS MUCOCILIARY CLEARANCE AND EVALUATION OF POSTOPERATIVE FRONTAL OSTIUM NEO-OSTEOGENESIS AND RESTENOSIS IN AN ANIMAL MODEL

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The modified endoscopic Lothrop (MEL) procedure has been advocated as an alternative to the more invasive osteoplastic flap with obliteration for management of frontal sinus disease. Little is known about the effects of the MEL procedure on frontal sinus mucociliary clearance. All patients have postoperative narrowing of the frontal sinus ostium, however it is not known whether neo-osteogenesis occurs or if indeed it affects mucociliary clearance. 14 sheep underwent the MEL procedure. Frontal sinus mucociliary clearance time measurements by nuclear medicine gamma scintigraphy via mini-trephines were performed preoperatively and 3 months postoperatively. The subjects were randomised with regard to the use of postoperative irrigation via mini-trephines. Sizes of frontal ostia were measured at 224 days postoperatively and biopsies taken from the bone of the frontal ostium. There was a non-significant trend towards faster mucociliary clearance times postoperatively. The average preoperative mucociliary clearance half times at 15 and 30 minutes were 70 and 74 minutes respectively, compared with 50 and 67 minutes postoperatively. There was a trend towards faster clearance times in the postoperative irrigation group. The average size of the frontal ostium decreased by 28%. There was histological evidence of new bone formation in 56% of biopsies. The average size of frontal ostia decreased by 28% in the absence of neo-osteogenesis compared with 29% in the presence of neo-osteogenesis, with a non-significant trend towards slower clearance times in the presence of neo-osteogenesis.
The modified endoscopic Lothrop procedure has no adverse effect on mucociliary clearance as measured at 3 months postoperatively, the results suggesting a trend towards improved postoperative clearance times. Postoperative irrigation via mini-trephines shows a trend towards improved mucociliary clearance. There is no relationship between the degree of ostial restenosis and either the presence of neo-osteogenesis or change in mucociliary clearance. The presence of neo-osteogenesis is associated with a trend towards slower mucociliary clearance times.

Poster no. 28

EFFECT OF INTERPHASE-GAP AND PULSE-DURATION ON ELECTRICALLY EVOKED POTENTIALS IN DEAFENED GUINEA PIGS: OBJECTIVE MEASURES RELATED TO NEURAL SURVIVAL

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An experiment was carried out to investigate whether the effects of interphase gap and pulse duration on electrically-evoked potentials are correlated with neural survival in guinea pigs. The motivation for this work was the need for an objective measure of neural degeneration in cochlear implant users. Such a measure would enable research with implantees to see if individualized fitting using this information would improve clinical outcomes with a cochlear implant. Eighteen guinea pigs were deafened by co-administration of kanamycin and frusemide. Each animal was implanted with a 8-electrode array at 1, 4 or 12 weeks following deafening. Electrically-evoked auditory brainstem response (EABR) and compound action potential (ECAP) input/output functions were recorded in response to biphasic current pulses. The current change required to equalize EABR/ECAP amplitude when pulse duration was doubled from 104 to 208μs per phase, or interphase gap increased from 8 to 58μs, was measured. Following the completion of each experiment the animal was euthanased and the cochleae examined for auditory nerve survival. Typically, there was a reduction in the effect of changing pulse duration and interphase gap with increasing duration of deafness. A significant positive correlation was found between surviving neural density and the size of the effect of pulse duration (EABR $r = 0.66$, $p = 0.01$) and interphase gap (EABR $r = 0.72$, $p = 0.005$; ECAP $r = 0.81$, $p = 0.008$). These results, when applied to cochlear implantees, will provide a tool for investigating the role of neural survival against variations in performance with the implant.

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Poster no. 29

GENETIC FINGERPRINTS OF ORAL CANCER CORRELATE WITH CLINICAL PARAMETERS AND IDENTIFY GENES ASSOCIATED WITH ADVANCED STAGE TUMORS

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Background:
Oral Squamous Cell Carcinoma (OSCC) is a clinically heterogeneous disease. Patients with stage-matched tumors show differences in treatment response and outcome, suggesting that the current staging system lacks precision. Clearly novel approaches to tumor staging are required. Recent studies have shown that genetic fingerprints based on the expression of thousands of genes can be used to predict known subtypes of disease and thus may represent a potential role in the molecular staging of cancer.

Methods:
Genetic fingerprints based on the expression of 19,000 genes were generated for 20 OSCC's using microarray technology. Tumors were classified into groups based on the similarity of their respective fingerprints. These groups were correlated with the clinical parameters and significantly over expressed genes identified for groups of interest. The expression of these genes were validated by quantitative RT-PCR

Results:
Two groups were generated that correlated with T ($p=0.035$) and N ($p=0.035$) stage. Further analysis identified a subset of 23 significantly deregulated genes in the group containing more advanced tumors. The differential expression of six of these genes was validated by quantitative real-time RT-PCR, and a statistically significant correlation was found between over-expression of *CLDN1* and *GALNT6* genes and nodal metastasis ($p=0.027$).

Conclusion:
Despite the clinical heterogeneity of OSCC, genetic fingerprinting can identify distinct patterns of gene expression that correlate with clinical parameters. Over-expression of *CLDN1* and *GALNT6* genes may represent potential biomarkers for advanced stage disease. The application of this methodology represents an advance in the classification of these tumors, and may ultimately aid in the development of more tailored therapies and improved prognosis for oral carcinoma.