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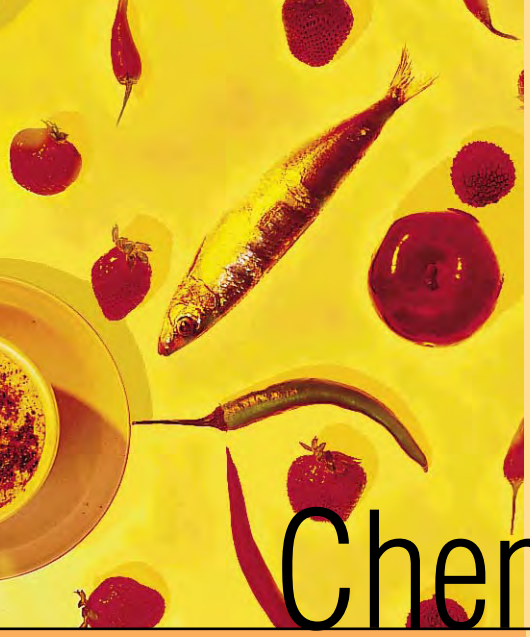

ChemoSense

EDITORIAL

A Nose for Discoveries

By Graham Bell
g.bell@e-nose.info

The objective of *ChemoSense* is to bring the important discoveries happening in the scientific field of the chemical senses to the world. Our readers include present and future leaders of industry and science. The review published in this issue meets our objectives and will delight all readers when they learn of the amazing journey of discovery taken by Alan MacKay-Sim and his colleagues in recent years. Their journey " up the nose" has led into a field of discovery "wider than the sky".

The first gathering of the Australasian chemosensory community held in New Zealand took place in December and was an acclaimed success. Follow the plans for the next AACSS scientific

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Adventures up the Nose

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Here is a tale about following your nose. How an innocent scientist interested in the neurobiology of olfactory function found himself "taking the path less travelled" from the friendly fields of olfactory neurogenesis to find himself in the middle of the scary woods of the neurobiology of brain diseases. The path from understanding the molecular and cellular bases of olfactory sensory neuron regeneration led to the adult stem cells of the human olfactory mucosa, and from there to olfactory stem cell as models for schizophrenia, Parkinson's disease and other less well known diseases affecting the nervous system, Hereditary Spastic Paraplegia and Ataxiatelangiectasia. Here is what I have learned: science does not travel in a straight line.

Neurogenesis in the Olfactory Epithelium

It is received wisdom in the olfactory biology community that the sensory neurons in the nose are replaced throughout life. This was first observed in the 1930's and 1940's in rabbits and monkeys, originally through experiments to destroy the olfactory organ as a conduit for the polio virus to reach the brain(1-3). It was even

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EDITORIAL CONTINUED

A Nose for Discoveries

continued

meeting in the coming issues of *ChemoSense*.

We welcome the return of Brian Crowley in the role of advertising manager for *ChemoSense*. Please contact him now, for a great "special deal" on advertising in this bulletin: crowbrin@hotmail.com ■

Adventures up the Nose

continued

used for this purpose as a public health initiative for a while. (This was the era of casual psychosurgery and frontal lobotomies.) Cell proliferation and sensory neuron replacement are found in all vertebrates studied, including primates(4). Although sensory neurons were thought to have a limited lifespan and replaced automatically (5), we now appreciate that that neurogenesis in the adult olfactory epithelium is a highly regulated process (6, 7). There is debate about the identity of the stem cell in the olfactory epithelium and the lineage of defined cell types that lead from stem cell to sensory neuron(8, 9). This lineage is maintained by cell proliferation of several cell types and regulated differentiation from one cell type to the other along the lineage. There is an interesting literature on the genetic regulation of this lineage through a growing list of transcription factors(10). Similarly, there is a growing list of autocrine and paracrine growth factors and cytokines that regulate the populations of cell to maintain tissue homeostasis in health, disease and injury(11). The adult olfactory epithelium provides a very useful model for understanding these processes because it is accessible and can be manipulated in vivo and in vitro. It is providing an understanding of the molecular and cellular regulation of neurogenesis applicable to the developing and adult nervous system. There are still many questions remaining to be answered on the mechanisms of olfactory epithelial neurogenesis that will require a deeper understanding of regulatory networks (12).

Stem Cells in the Olfactory Mucosa

For many years the debate has raged about the "true" stem cell of the olfactory epithelium. Following the lead from the field of hematopoeisis, the stem cell can be defined as a "slowly dividing" cell that "retains a DNA label for a long period", that divides asymmetrically to produce another stem cell and a daughter cell that is committed to differentiate. This describes cells on the basement membrane, horizontal basal cells (13). The daughter cell that is committed to differentiate continues to divide, but it is considered to divide symmetrically, producing daughter cells that are more or less equal. These are often referred to as "multi-potent progenitors" or "transit amplifying cells" (14). They may undergo several rounds of cell division before differentiating. Those undergoing their final proliferation before differentiating are known as "proliferating precursors" or "immediate neural precursors"(15). A current consensus is that both horizontal basal cells and globose basal cells can give rise to sensory neurons, supporting cells and Bowman's gland cells and ducts, as well as each other, contradicting the expectation of a unidirectional "lineage" (8, 16). This concept is resolved by considering the horizontal basal cells as a reservoir of quiescent stem cells that are only brought into play after massive damage to the olfactory epithelium with the globose basal cells normally regenerating the epithelium (9, 17).

Could the "true stem cell" still be unidentified? All experiments to date have studied populations of cells and their progeny. It is possible that a rare stem cell could be located among the globose or horizontal basal cells, unlabelled by the markers used to identify them, unnoticed without positive selection. Considering the multiple levels of multi-potent

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Adventures up the Nose

continued

proliferating precursors in the hematopoietic lineage, it is possible that there may be undiscovered stem cell candidates in the olfactory epithelium. A final decision on the hematopoietic stem cell lineage was only achieved with an assay in which single cells were shown to be able to reconstitute the whole hematopoietic system after otherwise lethal bone marrow irradiation and their progeny able to repeat the feat.

Neural stem cells are typically grown in vitro in media containing epithelial growth factor (EGF) and basic fibroblast growth factor (FGF2). This leads to cultures of tightly packed spheres of cells known as "neurospheres". Typically these are "tripotent", able to give rise to neurons, astrocytes and oligodendrocytes (18). Neurospheres can be generated from olfactory epithelium giving rise to epithelial cell types (19, 20) and neurospheres generated from olfactory mucosa are multipotent, generating non-epithelial and non-neural cell types (21, 22), raising the concept that this multipotency may arise from the neural crest origin on these multipotent stem cells (23). The therapeutic utility of olfactory stem cells has been shown in animal models of spinal cord injury (24), Parkinson's disease (25) and vertebral disc injury (26).

Human Olfactory Stem Cells as Models for Brain Diseases

The human olfactory mucosa is accessible via a relatively simple medical procedure under local or general anesthetic (Figure 1). As in mouse and rat, neural stem cells from the human olfactory mucosa are multipotent, giving rise to many non-neural cell types in vitro and when transplanted into the chick embryo (22). This makes the human olfactory mucosa an accessible tissue (27) that can provide multi-potent stem cells not only for cell transplantation therapies but also, when taken from patients, as cellular models of brain diseases. Stem cells from patients with diseases could be a very useful model because they could be propagated in culture, potentially in large numbers, and could be differentiated into the cell type of interest, for example neurons and glia. Realising that we could grow olfactory stem cells, and that olfactory cells show disease related cell biologies, we developed olfactory stem cells as models of brain diseases (28). We now have a bank of human olfactory stem cells from over 200 people, healthy controls and persons with various brain diseases (Figure 2).

Our approach is to compare olfactory stem cell cultures from multiple patients and multiple controls to discover what is shared by the patients that is different from the controls (28). The initial analysis of gene expression is "unbiased" or "hypothesis-free" to identify the cell signalling pathways that are regulated differently in patient cells compared to controls. We then target subsequent functional analyses of specific cell functions and identified signalling pathways. For example, in schizophrenia, dysregulated gene expression in patient cells was overwhelmingly concentrated neurodevelopmental pathways. Dysregulated gene expression in Parkinson's patient cells was concentrated in mitochondrial function and oxidative stress pathways. In each disease, the identified dysregulated functions are consistent with other genetic and epidemiological evidence and studies of post mortem brains, so gene expression profiling gives us "proof-of-principle" by leading us to cell functions already implicated in these

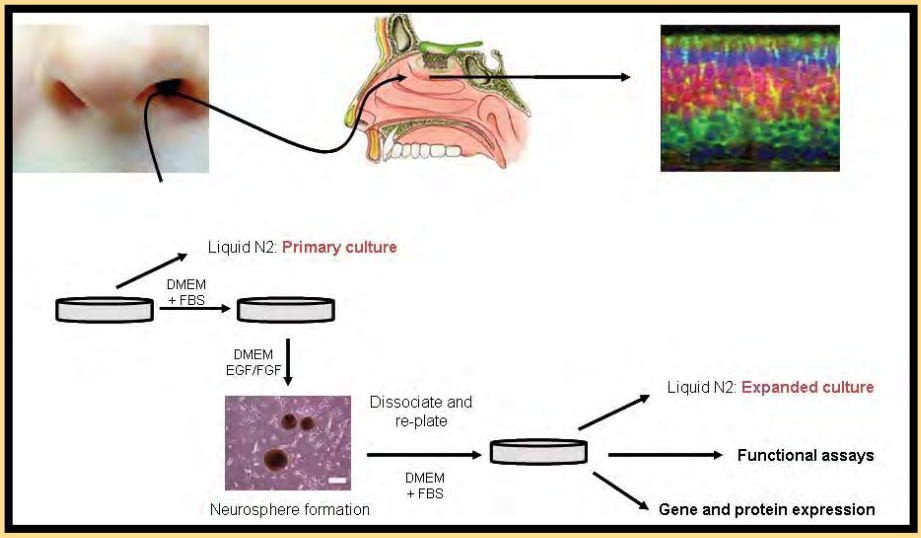

Figure 1. Culturing and banking human olfactory neural stem cells

Olffactory mucosa is obtained by biopsy through the nostril, under local anesthetic, by an otorhinolaryngologist. The mucosa (top right) is dissociated into single cells and grown for a week in culture medium (DMEM) with 10% fetal calf serum (FBS). These "primary" cultures can be frozen and stored in liquid nitrogen (liquid N2) or they are grown in DMEM plus growth factors (EGF/FGF) to generate "neurospheres" containing neural stem cells. The neurospheres are harvested 4-10 days later, dissociated into single cells and grown for many generations as "neurosphere-derived, expanded cultures" in DMEM + FBS. They are stored frozen in our "Neurobank" of olfactory stem cells and can be thawed for multiple assays.

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Adventures up the Nose

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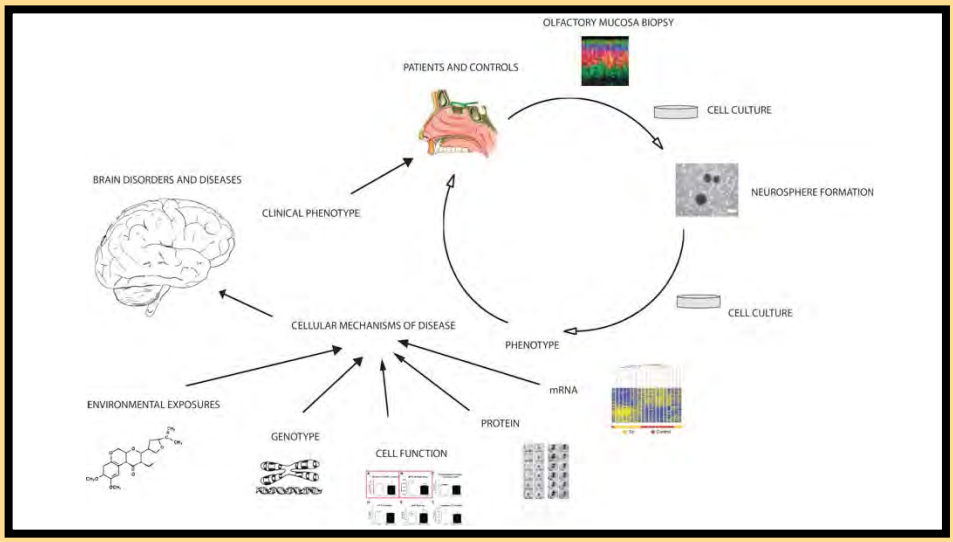

Figure 2. Olfactory neural stem cells as models for brain diseases

Patients with brain disease, and healthy controls, are identified clinically and their olfactory stem cells are generated and banked down. Patient-derived olfactory stem cells are then compared with those from healthy controls in a variety of assays – gene expression (mRNA), protein expression, cell functions, genotype (DNA) and drug or chemical exposures. Our Neurobank contains olfactory stem cells from 200 people, including patients with Schizophrenia, Parkinson's disease, Hereditary Spastic Paraplegia, Motor Neuron Disease, Mitochondrial Diseases, Ataxiatelangiectasia and others, as well as healthy controls. This biobank is coupled with databases of clinical and demographic data of each patient, as well as genomic and functional data generated through our experiments.

The concept that cells in the olfactory epithelium may reflect disease-status was developed through culture of "neuroblasts" from olfactory mucosa from patients with Alzheimer's disease (29). Primary cultures of olfactory epithelium from patients with schizophrenia had more proliferating cells than cultures from healthy controls (30). This was specific for schizophrenia and not the related psychosis, bipolar disorder (31). Bipolar patients had significantly more cell death in the cultures but the same cell proliferation as controls (31). Histological analysis of developing neurons and mature neurons in the post-mortem olfactory epithelium also showed alterations in the ratio of different cell types that is consistent with altered neurogenesis (32).

diseases. The advantage is that we now have specific molecular pathways to investigate and we can devise specific functional assays. In schizophrenia this has led us to show that patients' cells have increased cyclin D1, E and A2 levels, proteins that control the length of the cell cycle (33). This leads to a faster cell cycle and faster proliferation rate in patient cells compared to controls. In Parkinson's disease we identified dysfunction in the antioxidant pathway regulated by a transcription factor NRF2. Upon functional examination we found that drug activation of NRF2 restored patient cells to control levels, reducing the molecular signs of oxidative stress (34). These examples show how we can go from patient's cells to identifying altered cell functions to candidate drugs that restore patient cell functions to control levels. These cell models give a molecular insight into cellular mechanisms of broad disease hypotheses such as a "neurodevelopmental" origin of schizophrenia and "oxidative stress" being responsible for Parkinson's disease. Moreover, for diseases like these, for which causative genes have not been found, these cellular models give an insight into how cell dysfunction, and by implication disease, can arise from biological differences that are not measurable as genetic alterations in the DNA.

Olfactory stem cell models are applicable potentially to all neurological conditions and brain diseases. Olfactory biopsies can be obtained from adults and children and from patients with diseases caused by single genetic mutations. With collaborators we are working on cells from patients with MELAS, caused by a mutation in a mitochondrial gene, and from patients with ataxia telangiectasia, caused by a gene involved in DNA repair. Olfactory stem cells have been generated from patients with familial dysautonomia (35). For some diseases deep insights will be gained from olfactory cells from patients with known mutations and with unknown mutations and the same clinical signs and symptoms (36).

Therapeutic Potential of Olfactory Ensheathing Cells

The other cells from olfactory mucosa with exciting therapeutic potential are the olfactory ensheathing cells, the cells that surround the olfactory nerves as they pass from nose to brain. Their role in olfactory nerve regeneration was recognised as having potential to regenerate transected peripheral nerves into the spinal cord (37) and lesioned corticospinal tract axons (38). Our own studies concentrated on the olfactory ensheathing cells in the adult nose and their abilities to induce functional recovery after spinal cord transection and contusion injury (39-43). This led us to undertake a Phase I clinical trial to test the safety of transplanting autologous olfactory ensheathing cells into the injured spinal cord in humans paraplegics (44). Patients were followed for three years after transplantation and the procedure was deemed safe (45).

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Adventures up the Nose

continued

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NEWS

AACSS gets Sweet Taste of New Zealand

Richard Newcomb reports that the 13th Scientific meeting of the Australasian Association for ChemoSensory Science (AACSS) was held in Matakana, north of Auckland, New Zealand, from the 7-9 of December 2011. It was the first time the meeting has been held outside Australia. Over forty delegates assembled from Australia and New Zealand with invited speakers from Europe and the US. Wolfgang Meyerhof (German Institute of Human Nutrition) opened the meeting with a talk on bitter taste mechanisms at the molecular level, while Aidan Kiely (Yale University) spoke the following day on bitter taste from an insect perspective. Topics ranged from the molecular biology of chemosensory systems to sensory science in organisms including worms, insects, pigs and humans. Student prizes were awarded to Bernd Steinwender and Pablo German for talks on odorant and pheromone reception in insects. The conference was held in the spacious facilities at Ascension Winery. The dinner event provided a fine gustatory theme at Plume Restaurant and opportunities to sample world-famous New Zealand cuisine and wine.

The next AACSS meeting is being planned for Hamilton Island, Queensland, (or similar location) in July or August 2013. ChemoSense will carry a call for papers and other information when venue and dates have been decided ■

Delegates gather for AACSS in New Zealand, December 2011

ChemoSense

Media Kit

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ChemoSense is a quarterly bulletin dedicated to informing a broad international readership of the latest developments in the scientific field of the chemical senses: those senses such as smell and taste that translate molecular information into experience and behaviour. It is a field that crosses many disciplines and has an extremely wide range of applications. **ChemoSense** aims to inform intelligent people of the opportunities that chemosensory research offers.

By using this window on this crucial yet shy field of science and technology, readers will share the vision of the future that each mini-review, commentary and news item has to offer.

It has been the intention of the founders that **ChemoSense** should inspire more cash and supportive investment by industry, entrepreneurs and benefactors in this exciting field of knowledge-creation.

ChemoSense began in December 1998 as a publication of The Centre for ChemoSensory Research, of the University of New South Wales, in Sydney, Australia. In 2003 the University Centre closed and two companies spun out of it: E-Nose Pty Ltd, and Graham Bell and Associates Pty Ltd. These companies have shared the costs of producing ChemoSense since March 2003, when the publication changed from print to digital media.

ChemoSense now reaches over 4000 readers world-wide. Its contents are used as teaching materials in dozens of countries, and scientists and industrialists value the high quality of the writing, which makes cutting edge scientific information available to all.

In October 2008, the publication celebrated 10 years of existence and its 40th issue. Tributes from many key figures in the field of chemosensory science and technology are published in the October 2008 issue. Find all back issues at www.chemosense.info

Each issue of around 16 pages carries at least one mini-review, by invitation, from a leading person in a chemosensory area. They are asked to convey their unique perspective and experience on the subject and to present it in an easily read style. Ideas and suggestions for forthcoming articles are welcome: simply e-mail the editor,

Graham Bell, on g.bell@e-nose.info.

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25-28 April 2012	**AChemS XXXIV** Hyatt Huntington Beach, California www.achems.org
20-23 May 2012	**14th International Meeting on Chemical Sensors** Nuremberg, Germany www.icms2012.de
3-8 June 2012	**School on the Senses: Neurobiology & Behaviour** Bertinoro, Italy kathyann.koralek@gmail.com
4-7 June 2012	**ISOCS Short Course (Summer)** Nanotechnologies for Chemical Trace Detection Tarragona, Spain www.olfactionsociety.org
23-27 June 2012	**ISOT 2012 (with ECRO XXII)** Stockholm, Sweden administration@ISOTXVI.com
10-13 July 2012	**11th Sensometric Meeting** Rennes, France www.sensometric.org

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