

UNLOCKING

breast cancer's

SECRETS

FROM REFUGEE BEGINNINGS, PROFESSOR SUNIL LAKHANI HAS GONE ON TO PLAY A KEY ROLE IN CANCER RESEARCH, WRITES PETER LAVELLE.

PHOTOGRAPHER: ANDREW PORFYRI

Who'd have thought the study of abnormal breast tissue would owe so much to Idi Amin?

Born in Tanzania, raised in Uganda and expelled from that country in 1971 with his family and the rest of the population of Indian background, 12-year-old refugee Sunil Lakhani found sanctuary in Britain.

"My father was a doctor, so once we got to the UK he managed to get a job fairly quickly, in a very small conservative

rural village called West Rudham, in Norfolk," he says.

While it's hardly the done thing today, in Uganda the young Sunil had spent much of his early childhood sitting on the shoulders of anaesthetists while watching his father operate.

"I essentially grew up from an early age, about two or three, knowing that medicine was what I would do. I watched my first Caesarean at age four, when I discovered where babies come from!"

From a local grammar school in Fakenham, Norfolk, the future pathologist moved to London to study undergraduate medicine at St George's Hospital Medical School, south of the Thames.

"I also did most of my postgraduate training in a group of hospitals in South London – St George's, St Helier, Bolingboke Hospital, Kingston Hospital and the Royal Marsden," he says.

Pathology interested Professor Lakhani from the start. "I knew as soon as I started

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medicine that pathology was what I was going to do. What fascinated me most was physiology, and I realised fairly quickly that disease was essentially pathophysiology.”

After his internship, he didn't want to go into pathology straight away. “It was obvious that the clinical aspects of medicine were very strongly allied to pathology, and knowing clinical medicine well would help me to become a good pathologist.

“So I spent a few years doing general medicine, rotating through various medical specialities like oncology, renal medicine, geriatrics and intensive care.”

He had also developed by this time an interest in research. As an undergraduate, he had done BSc research in reproductive neurophysiology. He spent an elective at the Wellcome Metabolic Unit in Kingston, Jamaica, investigating acidosis, or excess acid, in malnourished babies.

And as an intern, while rotating through general medicine, he became involved in other small research projects, notably a study into the effects of combination chemotherapy on malignant melanoma patients.

In 1987, Professor Lakhani started his main pathology training at St George's, St Helier and the Royal Marsden hospitals. It was at the Royal Marsden that he became particularly interested in breast pathology, thanks to his mentor, Professor John Sloane, an internationally recognised breast pathologist.

“He knew I was interested in research, so he asked me to join his team and to work with a colleague at the Institute of Cancer Research, Professor Michael Stratton, a world-renowned molecular biologist.”

The team embarked upon a project trying to integrate aspects of breast pathology with molecular biology.

“We began looking at the early lesions that were being identified as part of the Breast Screening program in the UK,” Professor Lakhani says.

“Although the rationale for the screening program was to pick up an invasive cancer when it was still small and hence improve the woman's survival, the program was picking up lesions even earlier, before they were fully cancerous. Unfortunately, this made life for pathologists very hard as the biology and natural history of these lesions was unknown.

“So we decided to combine our pathology and molecular expertise to look at the relationship of these early lesions to breast cancer, so that we might one day learn how patients with precancerous lesions might best be managed.”

Their approach was to try to work out the developmental pathway from normal cell to cancer cell.

“We were looking at the regions of the chromosomes which were altered during the development from normal breast cells to cancer cells via these intermediate lesions - mutations at various chromosomal locations.

“We wanted to see what those mutations were and how they compared to patterns of mutations in invasive cancer. This might give us clues about how early or late a particular lesion was in the progression from normal breast to cancerous breast.”

At the time, they were mainly using a technique called LOH (loss of heterozygosity) to examine these mutations. This involved examining repetitive segments of DNA at a particular chromosomal position and comparing the segments at the same position in normal and lesion cells to see if a segment had been lost or altered.

“The questions we were interested in were: were segments of the chromosomes that were being lost in cancer cells also being lost in earlier precancerous lesions? Was there really evidence of progression at the molecular level?

“By dissecting these lesions out and examining them with techniques like LOH, we were able to determine that many of the changes found in cancer cells were also there in early precancerous lesions.”

They were present even in some tissues that appeared normal through the microscope but were in fact already along the path from normal to cancerous.

“Since then, we've been refining our understanding of these lesions using newer technologies such as conventional and micro-array-based comparative genomic hybridisation (CGH)”, Professor Lakhani says. “These give us further insights into the relationships between the early precancerous lesions and invasive cancer, and how a cell takes its first step to becoming cancerous.”

The group was also involved in the study of familial breast cancer.

“We were part of a European consortium called the Breast Cancer Linkage Consortium (BCLC), which played a major role in the localisation of the first predisposition (to breast cancer) gene, BRCA1 on chromosome 17, which was subsequently cloned in 1994.”

A year later, a second gene, BRCA2, was identified by a group that included Mike Stratton and Alan Ashworth at the Institute of Cancer Research.

“When these genes were identified, it provided a unique opportunity to look at the pathology of tumours that arise in patients who have mutations in these genes,” Professor Lakhani explains.

For the past 10 years, Professor Lakhani has been chair of the pathology group of the BCLC.



Professor Lakhani with members of his research team from the Queensland Institute of Medical Research

“We’re looking at how these tumours differ from other types of breast cancers, and we know for instance that BRCA1 tumours have some very distinctive features.”

They look more aggressive but whether they actually behave more aggressively remains controversial, he says.

The findings have clinical applications because a young patient with a cancer showing the relevant features has an increased risk of carrying a mutation in BRCA1 and hence may benefit from being tested for it.

Another area of research the group has undertaken is the study of breast cancers with what is known as myoepithelial differentiation. Whether these tumours truly arise from the breast’s myoepithelial cells is unknown.

“There is little doubt that these tumours are different to other breast cancers in their morphology and behaviour and so they may need to be treated

differently – currently they are not,” Professor Lakhani says.

Chairing the pathology group at the BCLC was to have some unexpected personal benefits for Professor Lakhani. In 2003 he was invited by kConFab (the Kathleen Cunningham Foundation Consortium for research into familial breast and breast plus ovarian cancer) to address its annual meeting on South Stradbroke Island in Queensland.

He took his wife and two children, aged 10 and 12, along for a holiday. While on the trip, he learned that the chair of pathology at the University of Queensland was vacant.

“As a bit of a joke, some colleagues suggested I ought to put my hand up,” he says. Twelve months later he migrated to Brisbane with his family and some of his research staff!

Professor Lakhani is now Head of Molecular and Cellular Pathology at the university’s School of Medicine, as well as being Head of the Molecular Pathology

Laboratory and Honorary Principal Research Fellow at the Queensland Institute of Medical Research, where he is continuing his research with the staff who relocated with him.

The professor is also an affiliate of global cancer network the Ludwig Institute for Cancer Research, which has funded clinical fellowships in his laboratory to train the next generation of academic pathologists. He is continuing his clinical work as a visiting specialist at the Royal Brisbane and Women’s Hospital, where together with his clinical colleagues, he provides a statewide service in breast pathology.

In late 2004 Professor Lakhani was awarded Fellowship of the Royal College of Pathologists of Australasia.

It’s all a long way from the dirt roads of Uganda. 📍

Professor Lakhani will speak on the use of molecular pathology in the diagnosis of breast disease on Sunday 12th March at Pathology Update.
