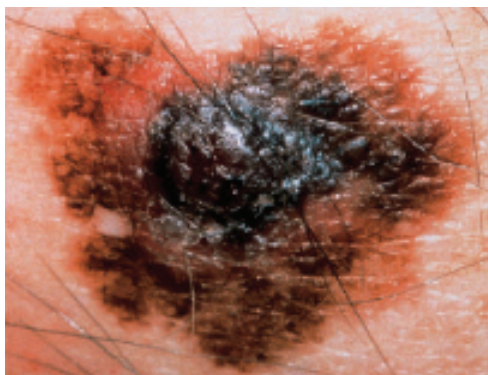


CANCERS OF THE SKIN



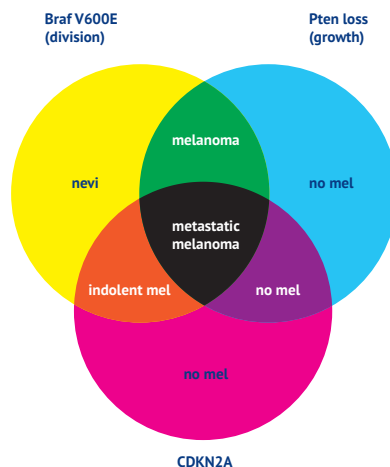
Melanoma – the fastest rising cancer in the UK

Melanoma has been the fastest rising cancer in the UK over the past 25 years, with more than 12,000 cases a year and 2,000 deaths. Death rates are 7 per cent higher in men although the incidence of the cancer is the same in both sexes.

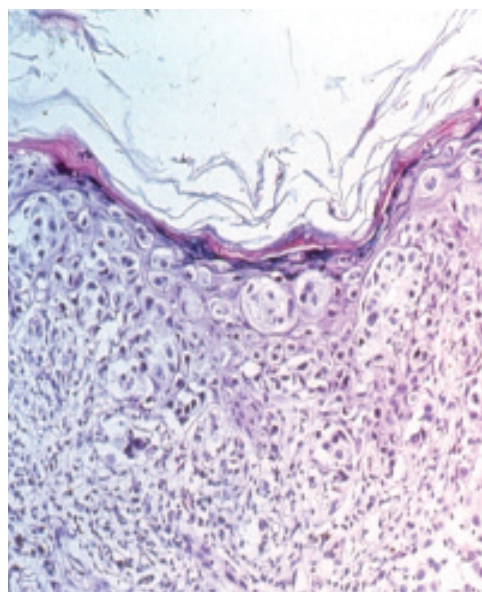
Until recently surgery to remove the lesions was the only treatment. But in June 2011, scientists unveiled what has been described as the biggest breakthrough in the treatment of melanoma in 30 years – a twice a day pill that halved the death rate among patients with advanced disease.

Melanoma is the deadliest form of skin cancer, killing one in five of those affected. A typical victim is the pale-skinned office worker who spends two weeks broiling on a Mediterranean beach until their skin is red and blistered.

Men tend to delay going to the doctor and may be more biologically susceptible which could explain their higher death rate. Covering up in the midday sun and using high-factor sun cream is the best defence against the cancer.



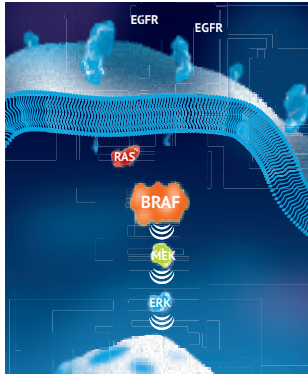
Three different mutations determine, in combination, whether melanoma is slow growing or capable of rapid spread



There are 12,000 cases of melanoma and 2,000 deaths a year



The typical victim of melanoma is a pale-skinned office worker who spends two weeks a year broiling on a Mediterranean beach till their skin is red and blistered.



Melanoma is driven by BRAF and NRAS gene mutations in the cell

New Drugs

The results of the international trial of the twice a day pill in which St John's was a key partner, showed the drug, vemurafenib, boosted survival rates at six months from 64 per cent to 84 per cent. The improvement was so dramatic that half way through the trial the patients randomly assigned to standard chemotherapy were offered the chance to switch to vemurafenib.

The drug is the first "personalised" treatment for melanoma, designed to target cases of the

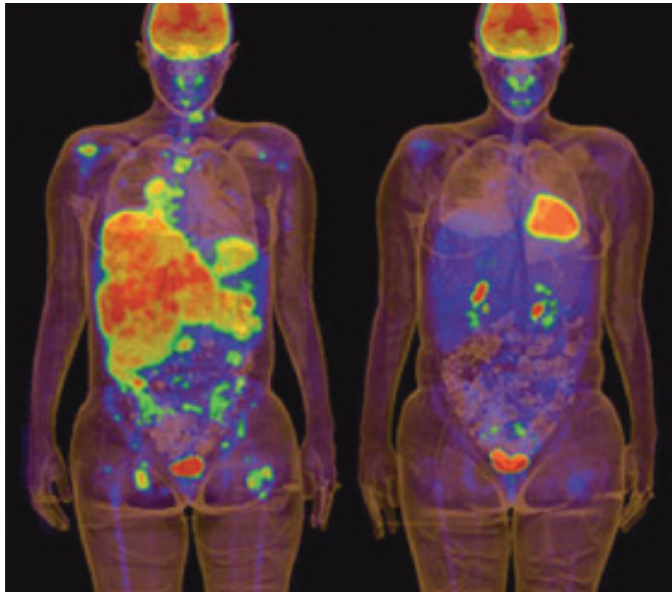
disease carrying the faulty gene, called a BRAF mutation, which account for about half of all cases. As such, it marks a milestone in the transformation of cancer medicines from blunderbuss treatments for everybody to designer drugs tailored to individual cases.

The findings were published in the New England Journal of Medicine and vemurafenib, marketed as Zelboraf by the multinational pharmaceutical company Roche, was licensed in Europe in 2013.

The development demonstrates the dividends

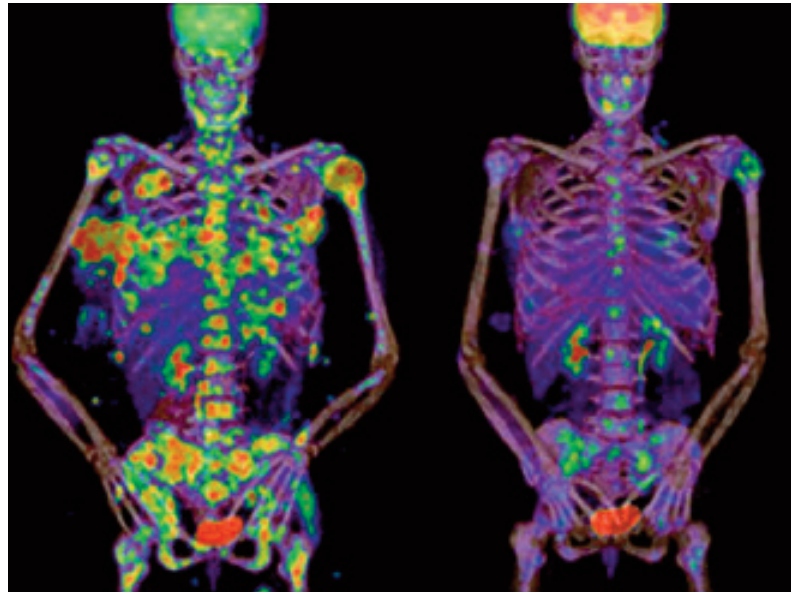
a Patient 1
Pre-treatment

2 weeks vemurafenib



b Patient 2
Pre-treatment

2 weeks vemurafenib



These scans show how the drug, vemurafenib, a BRAF inhibitor, reversed the disease in two patients. It has been described as the biggest breakthrough in the treatment of melanoma in 30 years.

that the collaborative spirit fostered by St Johns – across specialties and across the world - can bring.

The melanoma service was started at the Institute in the 1990s by **Neil Smith**, a dermatologist and skin pathologist who happened also to be an accomplished cartoonist. It combined plastic surgery and oncology with dermatology to create an early example of the multidisciplinary service that would become standard throughout the NHS over a decade later.

An early challenge was to understand why surgery to remove the lesions successfully halted the disease in some patients while in others it did not. In the 1970s, surgeons made enormous excisions, leaving unsightly scars, in their effort to rid the body of cancer. But the approach failed and today a border of just 1-2cm of healthy tissue around the lesion is removed.

Professor Sean Whittaker, head of the department, said: “The problem was for those patients who progressed we had no treatment. So the challenge was: could we identify who would progress and do something to help them?”



(From left to right) Edward Wilson-Jones, who developed dermatopathology at St John's, Peter Samman, founder of the lymphoma service, Neil Smith, who started the melanoma service and Margaret Spittle, the pioneer of radiotherapy for skin lymphomas in the UK



Cath Morgan



Sukran Sagham



Alison Baker

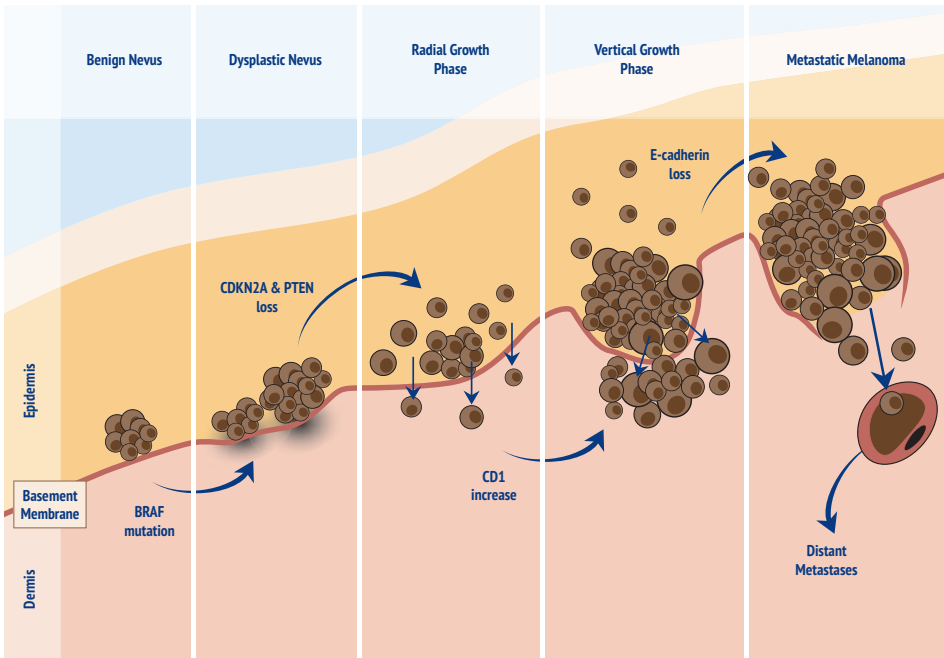


Ian Gosling

The Clinical Nurse Specialist (CNS) Team in our skin cancer department.



Moles (left to right)
Benign
Dysplastic
Melanoma



Development of melanoma showing how the disease breaks through the skin's basement membrane and spreads to other organs and distant parts of the body

A new diagnostic technique

St John's answer was to develop sentinel node biopsy, a technique now widely practised for determining how far melanoma has spread. Surgery is carried out in two stages, ten days apart, with the second operation designed to "sweep up" after the precise extent of the cancerous tissue has been confirmed in the laboratory after the first operation.

Before the second op goes ahead, surgeons inject blue dye with a radioactive tracer at four points around the scar. The tracer is taken up by the lymph glands and its location can be detected with a

geiger counter. Surgeons open an incision at that point to expose the pea-sized lymph gland coloured blue with the dye which is removed and checked to see if there is early spread of the cancer. If it is affected, all other lymph glands in the area are removed – a bigger operation with a higher risk of complications.

"Sentinel node biopsy is the most sensitive mechanism we have for predicting the spread of melanoma. If it is negative, the risk is low. If it is positive, the risk goes up substantially. The problem is that the therapeutic implications are limited," said Professor Whittaker.

Surgeons still do not know whether, where the technique indicates spread, removing all the glands is effective. A trial is currently underway but experts are pessimistic about the outcome. "It looks as if further surgery adds no further benefit, but we await the results," said Professor Whittaker.

Critics have argued that if there is no therapeutic potential there is no point in carrying out the test. But Professor Whittaker disagrees.

"Now we have new treatments for melanoma becoming available, accurate prognostic information is very important. We need to select the treatments most likely to benefit the patients."

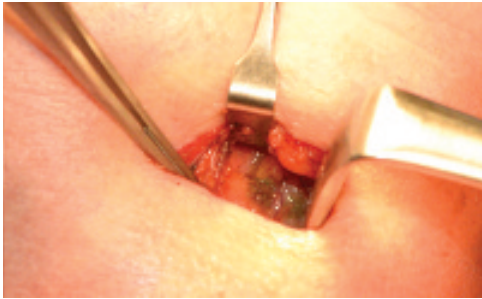
The latest development in sentinel node biopsy does away with the biopsy and replaces it with a sophisticated scanning technique called Spect CT Scanning. This involves taking two different types of scans and merging the images to provide more precise information about the location of affected lymph nodes.

The technique depends on a marker to identify tumour cells and is still under development. It is important because a patient with a melanoma on their back could find the cancer has spread to any one, or all, of six sites – two either side of the neck, under the arms or in the groin.

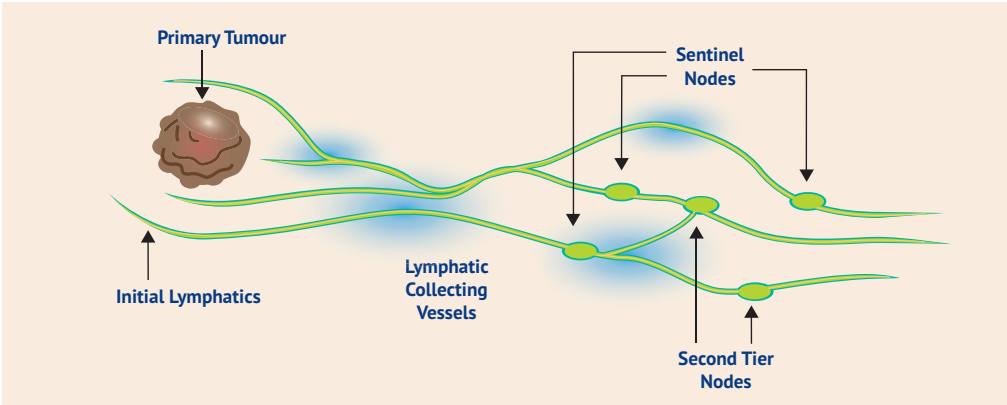
"The nightmare scenario is surgery required in all six sites. But this might be reduced to two with Spect CT scanning because it can look in a more sophisticated manner," said Professor Whittaker.



Lymphoma group: Sean Whittaker, Mary Wain, Stephen Morris, Fiona Child, Danuta Orlowska with colleagues.



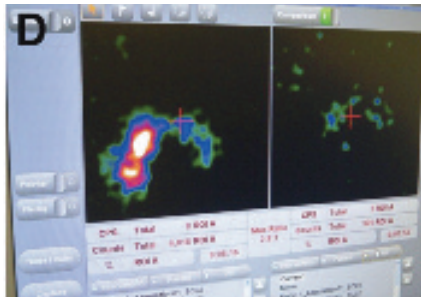
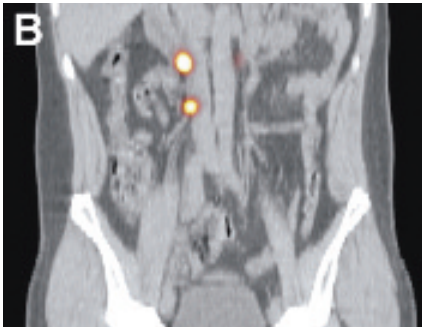
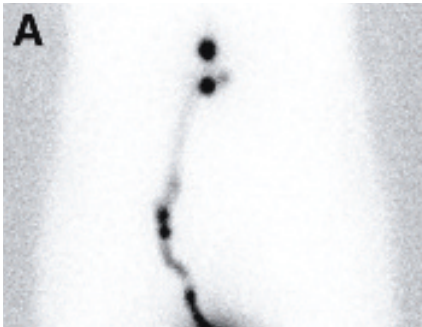
Lymph node biopsy: removal of pea-sized gland to check for cancer



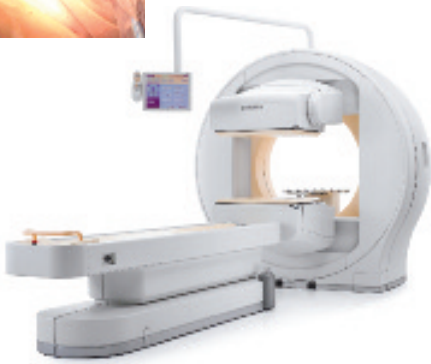
Sentinel Nodes Map: in some patients surgery to remove the primary tumour halts the disease. In others, it spreads through the lymphatic system. This map is used to trace its spread



If one lymph gland is affected the others are removed



Spect CT Scanning involves taking two different types of scans and merging the images to provide more precise information.



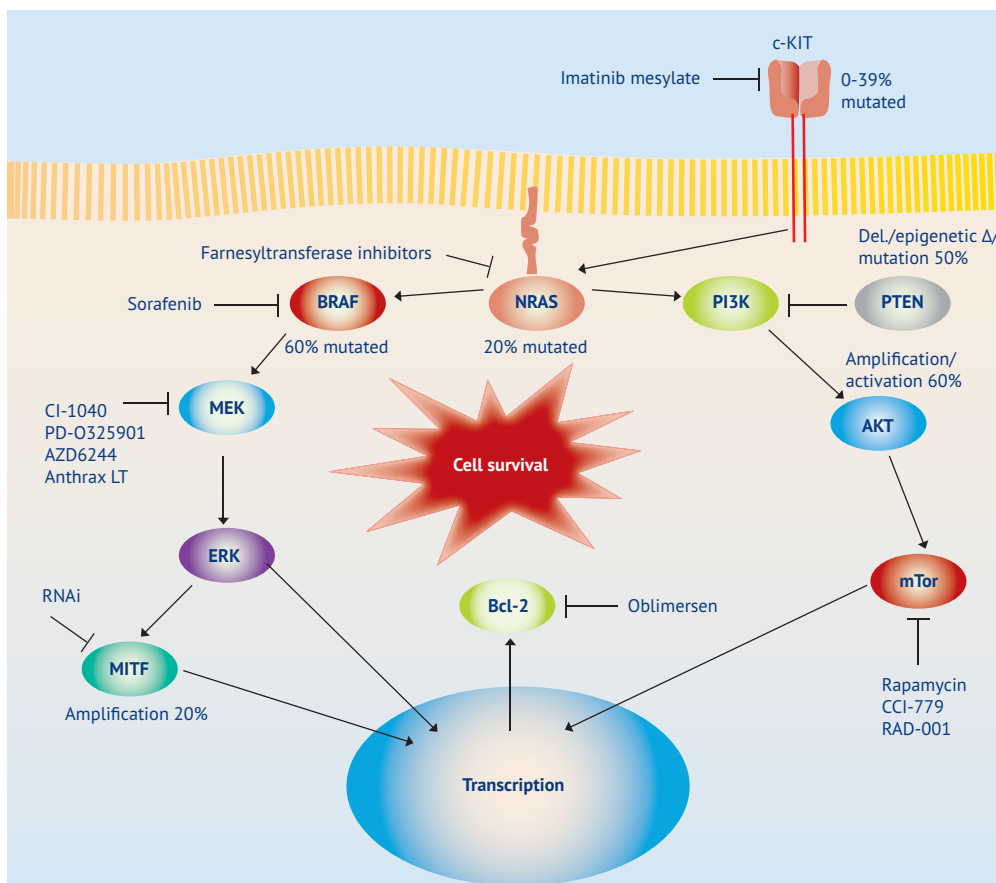
The Spect CT Scanner – a new technique for identifying the spread of cancer to the lymph nodes. It is still under development but could one day lead to more refined surgery

Genetic sequencing

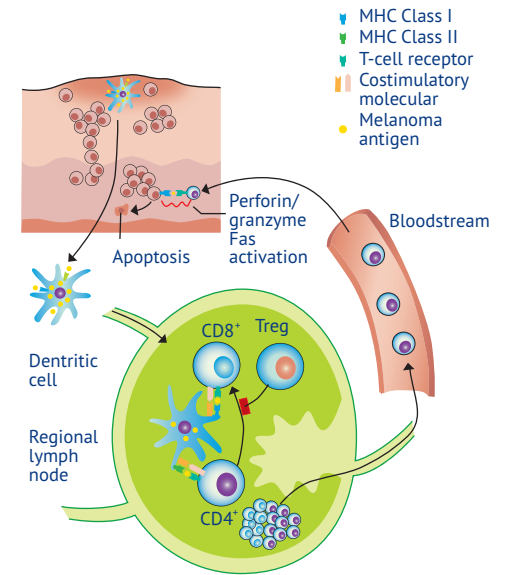
Genetic analysis has shown that 60 per cent of melanomas have a BRAF mutation and 20 per cent a NRAS mutation, turning the respective genes into cancer causing oncogenes. By identifying the genetic make-up of a patient's tumour, doctors can

select the right targeted treatment for it. Modern sequencing techniques allow this to be done.

In addition to the trial of vemurafenib, a targeted genetic therapy, St John's also participated in studies of immunotherapy – to boost the immune system and enhance its ability to destroy melanoma cells – with the drug ipilimumab, which was



Genetic sequencing has shown that 60 per cent of melanomas have a BRAF mutation and 20 per cent a NRAS mutation. By identifying the genetic make-up, doctors can target the cancer with the right treatment



Targeted immunotherapy has been pioneered at St John's for the worst affected cases and have brought long term benefit

licensed in Europe in 2011.

In one trial of the drug, made by Bristol Myers Squibb and marketed under the brand name Yervoy, survival at one year was almost doubled from 25 per cent to 46 per cent. However it is expensive at £72,000 for one course of treatment.

Further research is under way into developing antibodies against cancer cells that might be combined with immunotherapy, creating a synergy that enhances the effect of each treatment. The hope is to repeat the success achieved with rituximab in B-cell lymphoma which, when combined with chemotherapy, has proved remarkably effective.

Mole mapping

Melanoma often starts with changes to a mole and people with lots of moles and a family history of the disease are at higher risk, especially if they have clusters of abnormal-looking moles.

As a result researchers are developing a mole mapping service based on an algorithm which could serve as a screening technique.

The idea is that it could be used for high risk patients who would be screened twice a year and may need multiple moles removed. Early diagnosis is essential because if the tumour is less than 1mm thick the cure rate is 90 per cent. If it is over 4mm thick, the cure rate drops to 20 per cent.

But researchers must demonstrate that the algorithm is superior to a visual examination by a specialist.

Existing algorithms are based on criteria derived from visual inspections by experts and are skewed to ensure they are very safe. As a result a patient with many moles who is screened using the algorithm may be advised they need half a dozen removing while a specialist may say only one should be cut out.

For this reason the technique is of little value in screening people at normal risk

Tissue research

Key to any diagnosis of skin cancer, or indeed of any cancer, are the pathologists who check the tissue samples removed at biopsy or in surgery for signs of malignant cells.

St John's has built up a tissue bank of over 15,000



Katie Lacy examining a patient in her melanoma clinic

samples of all types of skin disease, especially melanoma and lymphoma, which has become a national resource.

All the samples, which include blood, lymph and skin, are of unused tissue taken for therapeutic or diagnostic reasons. They are retained for research only with the consent of the patient and are anonymised, categorised and ethically approved.

"It is very important that patients understand this – samples are never taken except as part of diagnosis or treatment. The unused portion may then be retained for research, but only with the consent of the patient," Professor Whittaker said.

Between 3,000 and 4,000 samples come from other hospitals in the UK and overseas and the tissue bank is the largest of its kind in the UK. It was developed in cancer before being extended to cover other areas such as psoriasis.



Mole mapping: melanoma often starts with changes to a mole



Consultant Dermatopathologists: Eduardo Calonje (head of service) and Catherine Stefanato at the microscope

Non-Melanoma skin cancers



St John's has the largest skin cancer tissue bank in the UK with over 15,000 samples

These are extremely common with 100,000 cases a year in the UK. The number has increased by more than a third in the past decade, partly as a result of improved registration but also from increased exposure to the sun and use of sunbeds.

However, over 90 per cent are curable, mostly with surgery to remove the lesion. The majority are *basal cell skin cancers* accounting for three quarters of the total. They impose a huge burden on the NHS.

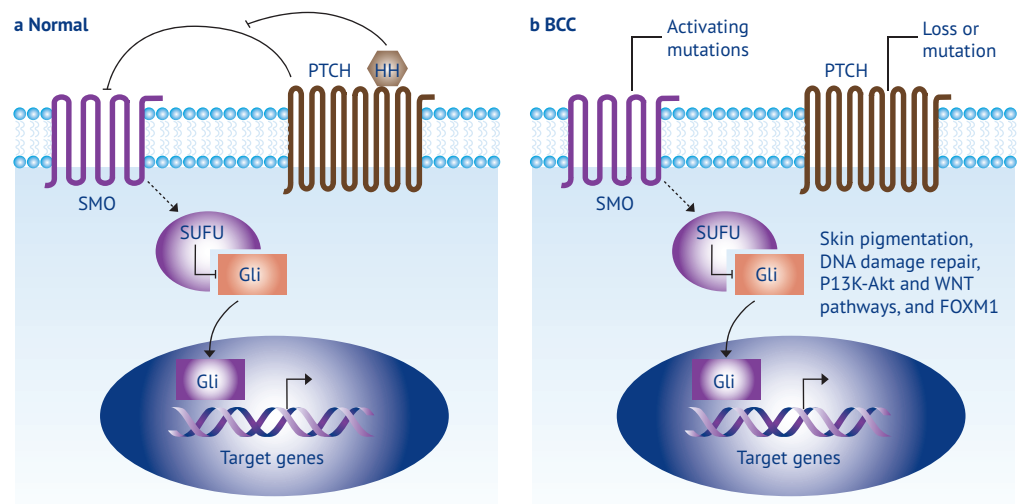
Some patients have a genetic predisposition to basal cell cancer and develop extensive lesions,

some of them large. In such cases surgical removal is difficult because of its mutilating effect.

Research has revealed the mechanism underlying basal cell cancer which is driven by a cluster of gene mutations and led to the development of a drug, vismogedib, which blocks the signal from the mutations and stops the cancer growing.

A topical version of the drug, which is applied directly to the skin, proved ineffective, but an oral version has cleared up lesions in patients with extensive disease. Vismogedib was licensed in Europe and the UK in 2013.

The samples are studied by dermatopathologists who have been critical to the success of the Cutaneous Oncology department. Advances in molecular pathology over the last 20 years have transformed the outlook for many patients and St John's is now exporting its expertise overseas. The institute has established international programmes for dermatopathology education in Europe, Asia and the Far East.



Hedgehog Signalling Pathway – this is implicated in the development of basal cell carcinoma, the commonest kind of skin cancer, with at least 75,000 cases a year

Cutaneous Lymphoma

This is a rare cancer of the lymphocytes (white blood cells) that primarily affects the skin. It is a kind of non-Hodgkin's lymphoma and affects 500-600 people a year in the UK of whom at least a third are treated at St John's.

It typically causes red, scaly skin patches similar to eczema or chronic dermatitis but a third of patients progress to more advanced disease. In severe cases extensive ulceration, itching and infections develop.

In its worst form, *cutaneous lymphoma* may lead to melon-sized tumours, involve the whole skin which becomes red and inflamed from top to toe, the hands swell and split and patients develop a leonine face. The lymph nodes and internal organs may also be affected.

The commonest type of cutaneous lymphoma is

Mycosis Fungoides. Paul Eddington, star of the 1980s TV sitcom "Yes, minister," was a sufferer.

Professor Whittaker said: "It can be a dreadful, Medieval disease – the worst affected patients have caused health workers to faint. They may have as many as 25 tumours the size of oranges on their skin which can be painful."

The disease is treatable but not curable and has a 35 per cent death rate. It is resistant to chemotherapy but susceptible to radiotherapy which is the mainstay of treatment.

An early pioneer of radiotherapy for the disease was **Margaret Spittle**, who became an iconic female



Margaret Spittle

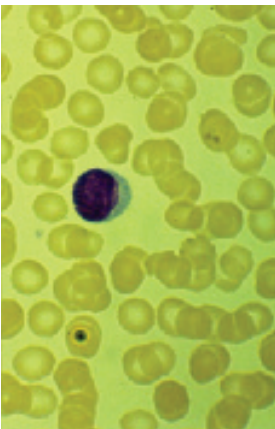
figure in the medical establishment. A Clinical Oncologist (radiotherapist) by training she went to Stanford University in California in the 1970s and returned with a technique of irradiating the whole body known as Total Skin Electron Beam Therapy (TSEB).

Professor Whittaker said: "There was a tradition at St John's of adopting specialists in other disciplines to work with dermatologists. The consultants felt isolated – so they looked for others with whom to work. That was part of how St John's became a multi-specialist discipline."

Electrons penetrate only 1mm into the skin so have a negligible impact on the underlying tissue. But administering TSEB is complex because bodies are curved and lumpy, requiring sophisticated physics.



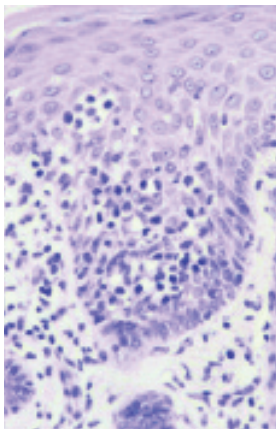
Abnormal chromosomes from a patient with a cutaneous lymphoma, a rare skin cancer affecting 500-600 people in the UK of whom one third are seen at St John's



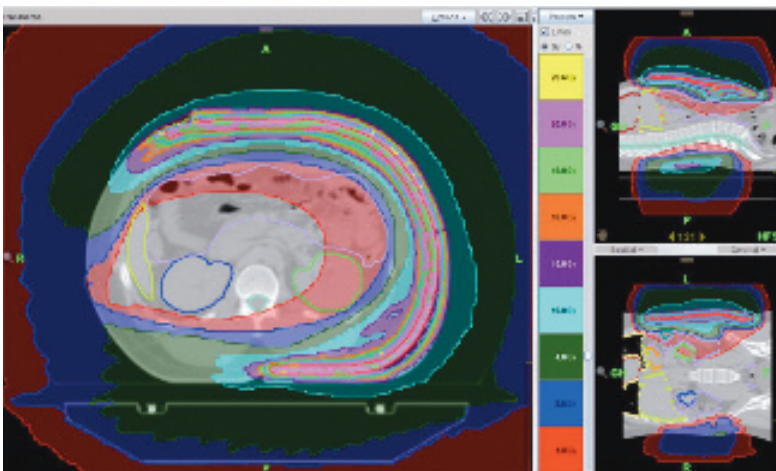
Cutaneous lymphoma cell in blood



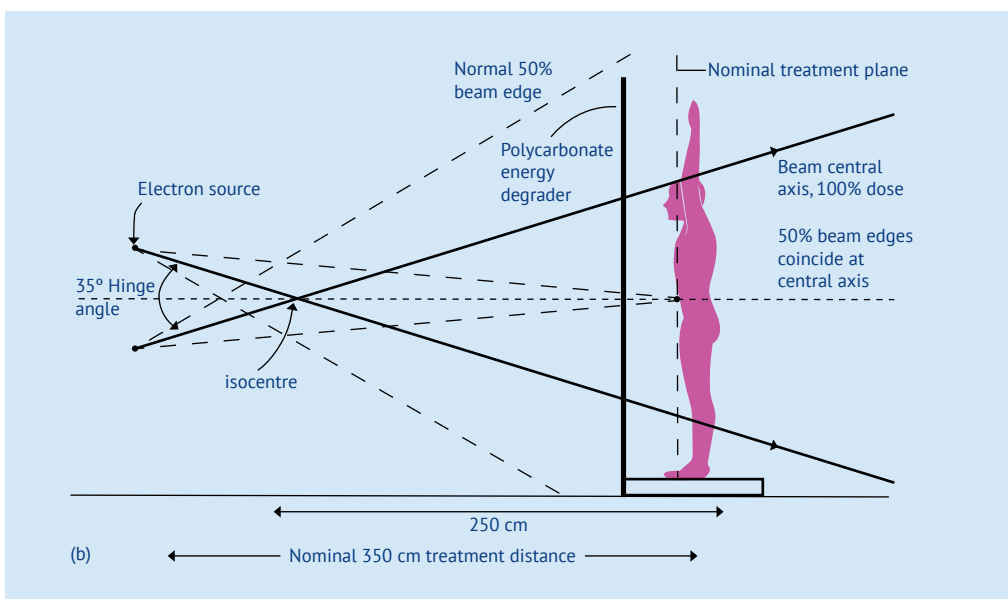
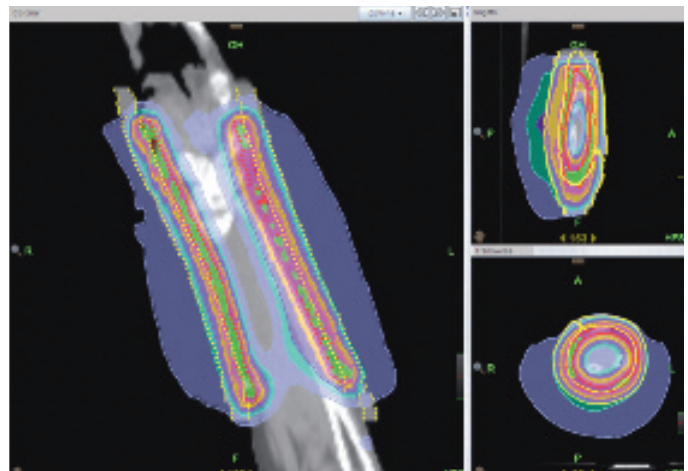
Electron microscopy image of abnormal nucleus



Lymphoma cells in skin



Tomotherapy for mycosis fungoides



Total Skin Electron Beam Therapy, a technique for irradiating the whole body, with a 95 per cent response rate in cutaneous lymphoma. Courtesy of Stephen Morris Consultant Clinical Oncologist who introduced TSEB to Guy's and St Thomas'.



The effect was dramatic. Within a few weeks of daily treatment, the skin cleared and patients recovered. They had to wear eye shields and lost their hair (and nails, unless they were protected). One side effect was that when hair grew back it was sometimes a different colour and texture – more like that from 30 years before.

But the main drawback was that the benefit did not last. The disease always returned – on average after 12 to 15 months. TSEB is also complex to administer – the machine must be reconfigured for each patient and the body rotated during treatment to ensure the skin gets an even dose across its surface. In the UK, St Johns is one of only three centres providing it (the others are Sheffield and Manchester).

Professor Whittaker said: “It is an extremely good palliative tool. The challenge is to maintain the response.”

Using the conventional dosage, patients are limited to one treatment in their lifetime because of the toxic effect on their skin. For this reason some experts say it should be reserved for people with advanced disease.

But a new low dose regime has been devised, which involves treatment for two weeks instead of five. As it is less toxic, the treatment can be administered every five to ten years.

“It is much better tolerated so it can be repeated. We trade a bit on the duration of the response but the overall response rate is still 95 per cent,” said Professor Whittaker.

New biologic drugs

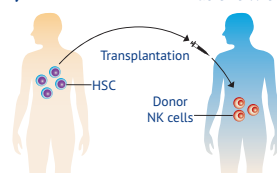
Cutaneous lymphoma tends to be resistant to chemotherapy. However, researchers are developing targeted biologic drugs that can damp down the disease.

Consultants from St John’s led an international trial of the first class of drugs to target the epigenetics of the condition, which acts like a shock absorber to calm down the abnormal genes driving the lymphoma cells. Two drugs – histone deacetylase inhibitors – have been approved by the Food and Drugs Administration (FDA) in the US. They are called vorinostat and depsipeptide. But the equivalent body,

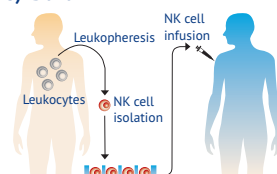
the European Medicines Agency (EMA) in the UK, has withheld a licence on the grounds that the improvement seen with the drugs is not significantly greater than with the standard treatment.

Professor Whittaker said: “We obtained a response rate of 38 per cent, with one in ten patients going into complete remission. But that was not sufficient for the EMA which claimed it was no better than the standard treatment. We say there is no standard treatment, response rates are low and we need multiple approaches. Some patients relapse early and need alternative treatments.”

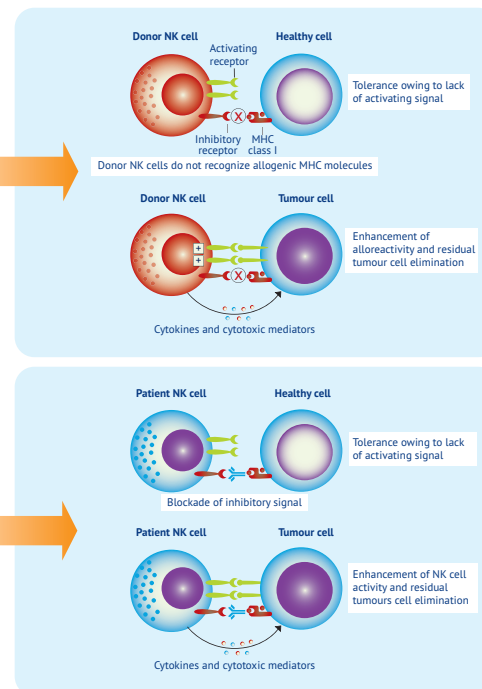
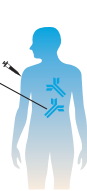
a) Donor Patient with cancer



b) Donor Patient with cancer



c) Monoclonal antibody specific for NK cell inhibitory receptor



Stem Cell Transplant

For the worst affected patients, a stem cell transplant is an option. St John's has pioneered this treatment which is still in the early stages of development. The treatment places a great strain on the body so patients must be under 60 with advanced disease and fit enough to withstand it. Blood is taken from a matched donor and stem cells extracted before being infused into the patient whose own immune system is first destroyed by chemotherapy (and sometimes radiotherapy).

If successful the patient will then start producing the immune cells of the donor which will fight the lymphoma. In some patients it has been highly successful. Professor Whittaker said: "It tells us that the use of immunotherapy can work. The mechanism is not understood but in some patients the treatment has brought long term benefit. Elucidating the mechanism could help the development of future treatments."

The danger is that the new immune system may perceive the body into which it has been transplanted as "foreign" and attack it in a life-threatening condition known as "graft vs host" disease. In year one of St John's transplant programme over a third of the patients died. Today the death rate stands at 15 per cent and is continuing to come down.

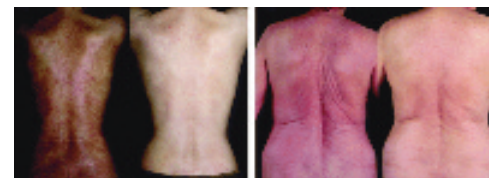
St John's is collaborating with Stanford University in California, US, on developing a protocol for stem cell transplants to improve results.

Photopheresis

This is a technique, used principally for treating chronic graft vs host disease and cutaneous lymphoma, that was pioneered in the UK by St Johns in the 1980s. It involves chemically treating blood with drugs that are activated by ultraviolet light. The blood is withdrawn from the patient, treated and then re-infused – hence, the full name of the procedure: extracorporeal photopheresis.

It was originally developed at Yale University in the US as a treatment for cutaneous lymphoma where the cancer is in the blood as well as the skin. This causes abnormal blood counts and the disease looks like leukaemia.

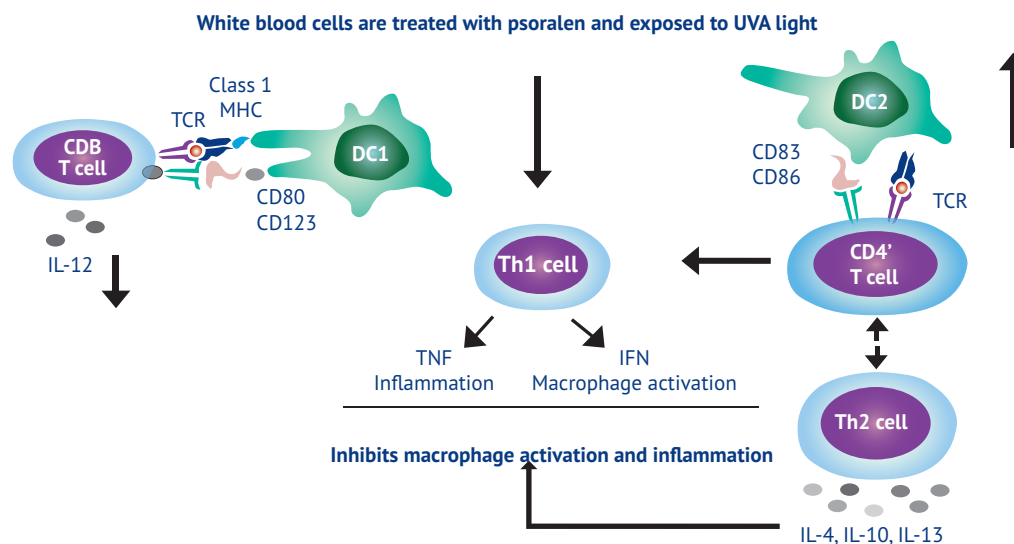
The skin is red all over and patients suffer with



Clinical treatment effect of extracorporeal photochemotherapy showing dramatic improvement

an excruciating itch. But patients treated with the technique every four weeks showed significant clinical benefit. It is thought to switch off part of the immune system but its mechanism of action is not understood.

Between 80-90 per cent of the patients treated at St John's with the method have chronic graft vs host disease, numbering more than 100 a month.



CASE STUDY - MARTIN GAMMON

Martin Gammon, 56, knows he is living on borrowed time – thanks to a new drug that brought him back from the brink of death.

In 2005 he mentioned to his GP that he had a mole on his back which was “itching a bit”. He was referred to the Queen Elizabeth hospital in Woolwich, south London, where he lived with his wife Yvonne, and was diagnosed with *melanoma*.

He was then 47. He had an operation to remove the mole and extensive tissue around it and later underwent sentinel node biopsy, the technique pioneered at St John’s.

It showed a lymph gland in his neck was affected which was removed. He had a couple of years respite and then the cancer returned in the form of a growth near the missing lymph gland. It was also removed.

Another year passed but in 2010, “things went downhill”. By 2011 he had been diagnosed with advanced (stage IV) melanoma.

“It was a death sentence. The doctor told me my life expectancy was three to six months. Between April and October tumours kept coming all over my body, from my legs to my head. I had 30 of them, including a brain tumour.”

He had a course of chemotherapy in September 2011, but it had no effect, apart from making him feel ill. Then he and Yvonne were shopping in BHS when he got a call from St John’s to say they had funding to try him on a drug, ipilimumab, a new form of immunotherapy which had just been licensed.

“I broke down and cried. It was like being offered



Martin Gammon with his late wife, Yvonne

a life raft. I said yes, I would try it.”

The first of four infusions of the drug – given three weeks apart – was administered in October and the second in November. Days later Martin and Yvonne got married – they had been together for a decade but had never ‘got round to it’ – and left on their honeymoon, a cruise round the Mediterranean and to the US. Unfortunately, Martin fell sick in Madeira and had to be flown home where he was admitted to hospital – a reaction to the immunotherapy. As a result, he missed the third infusion but was just about well enough to have the last one on schedule in December 2011.

“After that, I got worse and worse. In January we started making plans for my funeral. I thought that was it. Then, almost overnight, I started to get better. The tumours started shrinking, including the one in my brain (as shown on a scan). By March 2012, just about everything had gone, apart from those on my liver.”

In October 2012 he had an operation to remove part of his liver. Since then he has had no more treatment. Sadly, Yvonne died in 2014 but he remains well.

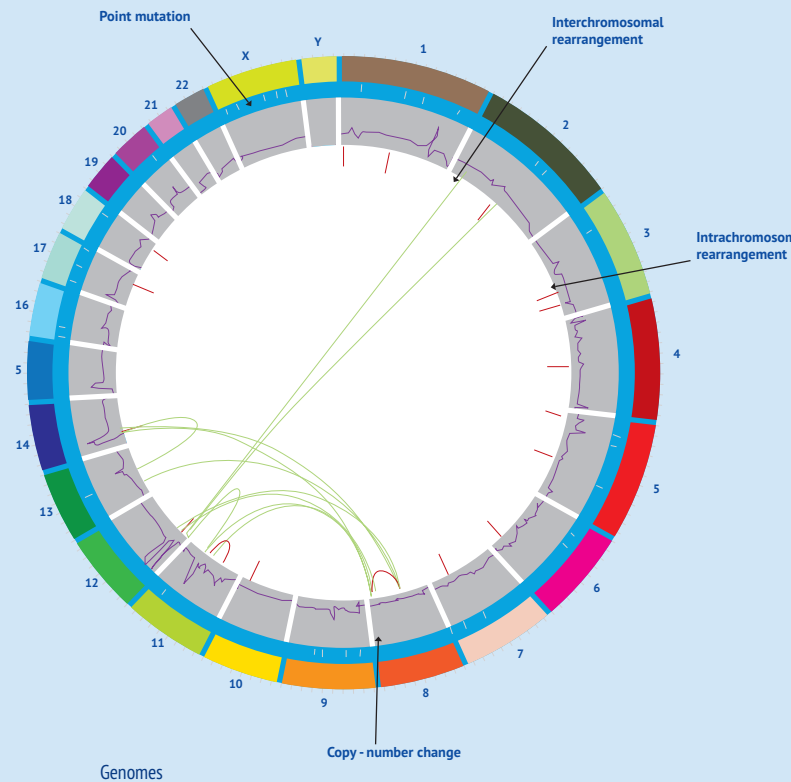
Nine years after being diagnosed with melanoma, he said: “I am one of the success stories. Without the drug I would have been in my grave for at least two years. It’s not a miracle cure – it doesn’t work for everybody. But if it works for you – that is what counts.”

The future

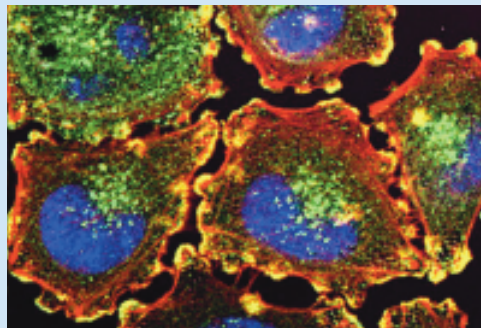
The basic research undertaken at St Johns is allied closely to patients needs. "It is not about stitching mice together," said Professor Whittaker.

Genes hold the key. Examining the genetic make-up of tumours for abnormalities and the prevalence of the mutations across a population is a major area of research for the future. There may be half a dozen genes that are important but establishing whether they are a necessary cause of the disease, or connected with each other, is the challenge.

Professor Whittaker said: "There has been little improvement in survival in 25 years but there are big potential gains on the horizon. We are caring for our patients better mainly due to the excellent compassionate care provided by our wonderful team of specialist skin cancer clinical nurse specialists and working to develop a more targeted approach to treatment based on tumour genome sequencing. That promises the next leap forward."



Genetic screening



Melanoma cell



Human Genome sequencing

