Implantable MicroSystems

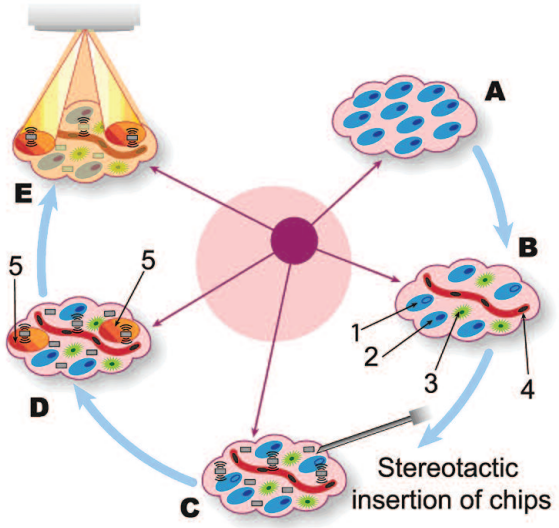
IMPACT *for* Personalised Anti-Cancer Therapy

Personalised cancer care: **electronic implants**

THE UNIVERSITY OF EDINBURGH

IMPACT is a 5-year, £5.2M research project (2012–2018) funded by an EPSRC Programme Grant to develop new approaches to cancer treatment. Using smart sensors fabricated on silicon in the University's IMNS Cleanroom Facilities, IMPACT will use wireless sensor chips implanted via a biopsy needle to monitor the real-time status of an individual tumour. This will allow radiotherapy (RT) to be targeted in space and time to maximise the disruption of cancer cell growth. The team consists of engineers, chemists, veterinary clinicians, social scientists and human cancer specialists, led by Prof Alan Murray from the University's School of Engineering.

Localised, solid cancers rely on a supply of oxygen and nutrition provided by the tumour microenvironment, and the chaotic blood supply of a tumour effectively outgrows its own oxygen supplies. The oxygen-starved cancer cells that result resist both RT and chemotherapy and these hypoxic regions are not static but change and move in time. This urgent, unmet clinical priority is the focus of IMPACT: to capture the rapid, highly-localised and transitory changes in hypoxia, pH and other key biomarkers such as proteins and nucleic acids which influence a tumour's local response to RT and chemotherapy. Hypoxia can be measured indirectly on tumour biopsies and by imaging, or directly by invasive probes but this does not capture vital, rapid changes in oxygenation and today's invasive probes are impractical in patients. IMPACT will be able to direct advanced RT technology, which is able to target higher doses of radiation treatment to selective areas of a tumour.



The diagram to the left shows the IMPACT principle.

A A group of cancer cells is identified for RT treatment.

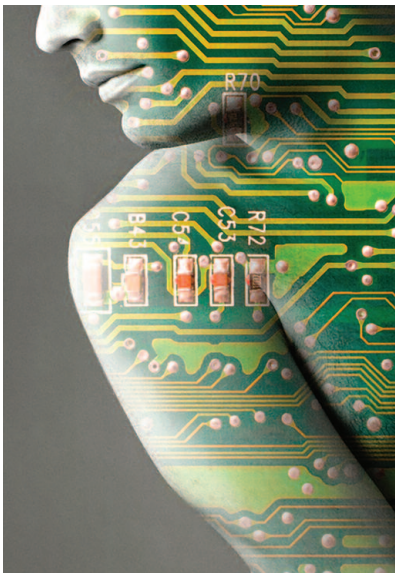
B This region contains RT-resistant cells (1), RT-sensitive cells (2), immune cells (3) and the blood supply (4) that form the tumour's microenvironment.

C Before treatment, sensor chips will be inserted stereotactically amongst this cluster of cells.

D The sensor chips will identify the RT-resistant regions (5) and relay this information to the radiotherapist.

E RT will then be aimed and timed to do maximum damage to the RT-resistant cancer cells.

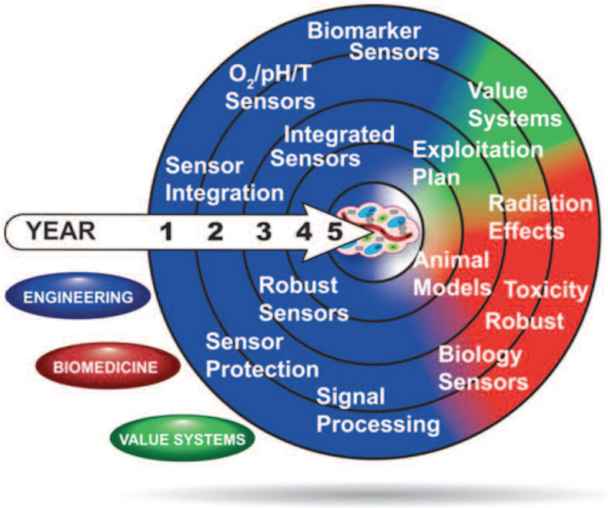
IMPACT's sensors will measure oxygen levels as well as more detailed biomarkers that indicate both the status of the tumour and the success of the highly-focussed RT. For example, enzymes called Caspases are often referred to as the 'executioners of cancer cell death' as they are present in large quantities when cancer cells rupture and die. The IMPACT device will measure their concentration to gather further intelligence on the success of RT in destroying the cancer. The IMPACT project also aims to ensure that this form of very personalised treatment is acceptable to both patients and their doctors, by consulting both groups and taking their views into account directly and in detail as the sensor-chip technology is developed. The IMPACT team has developed proof of principle and is now aiming to move the technology rapidly toward the clinic.



IMPACT's Research Challenges

IMPACT integrates sensitive, on-chip sensors with the instrumentation, control and communications that they require. The final choice of sensor technologies will depend upon: sensor responses and calibration, the size of the implanted device, techniques to fabricate sensors alongside standard integrated circuits, and chip packaging technology for long term implantation. Biomarkers directly implicated in cancer progression, as well as cancer cell death (through apoptosis or necrosis) will be targeted. These include Caspase-9, transcription factors such as hypoxia-inducible factors (HIFs) and the nucleic acids (specifically DNA) released by dying cells. For example, the caspases are ideal monitors of apoptosis. IMPACT's challenge is to detect relevant cancer biomarkers, specifically and sensitively. This approach will also be applicable generically to other protein and nucleic acid biomarkers, enabling a suite of specific biomarker sensors to be incorporated readily on chip.

Initially, IMPACT's implanted sensors are connected to the outside world via wires for power delivery and data transfer. This is undesirable due to the problems presented by wires exiting through the skin, so IMPACT is developing an implant that communicates via wireless power transfer. IMPACT's biosensor and instrumentation designs must address the challenges of low power operation, wireless communications and signal distortion by the hostile environment that is the human body.



The IMPACT team plans to submit a proposal to include delivery of chemotherapy in mid-2018 and a proposal for human clinical trials in late 2018.

IMPACT is now in its final year. Two types of oxygen sensor (Clark electrode and Ion-Sensitive Field Effect Transistor) have been developed, tested and miniaturised. These have been shown to work in continuous monitoring mode in live sheep. Biomarker sensors for key proteins implicated in cancer have been developed and tested and are now being miniaturised and integrated with CMOS silicon IC technology. We will also test these in live sheep later in 2018. All sensors have been found to survive sterilisation, implantation and subsequent radiotherapy.

Once the IMPACT platform of sensor circuits coupled to a wireless power/communications scheme is tested, it will be available for applications such as sensing of diseases other than cancer where real time, accurate (in space and time) monitoring may improve patient outcomes.

The IMPACT team:

Engineering	**Professor Alan Murray, Dr Brian Flynn, Dr Martin Reekie, Dr Stewart Smith, Dr Jon Terry, Professor Ian Underwood, Professor Steve McLaughlin (Heriot Watt University)**
Chemistry	**Professor Mark Bradley, Professor Andy Mount**
Veterinary Medicine	**Professor David Argyle**
Science, Technology and Innovation Studies	**Professor Joyce Tait, Dr Gill Haddow**
Molecular & Clinical Medicine, Edinburgh Cancer Centre	**Professor Ian Kunkler**
Clinical Research Imaging Centre	**Professor Edwin Van Beek**
NHS (Western General Hospital)	**Dr Duncan McLaren**
Oncology Physics, Edinburgh Cancer Centre	**Dr Bill Nailon**

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