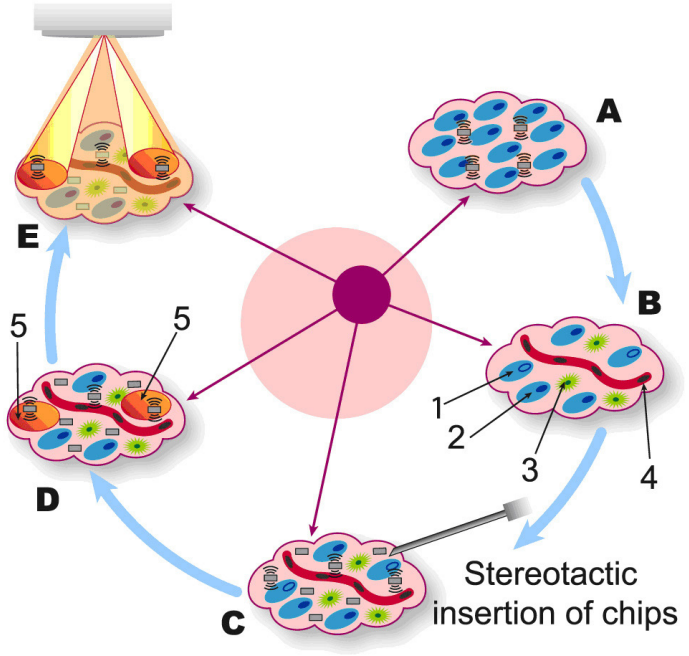
Implantable Microsystems

IMPACT *for* Personalised Anti-Cancer Therapy

IMPACT is a 5-year, £5.2M research project, funded by an EPSRC Programme Grant awarded to the University of Edinburgh to develop new approaches to cancer treatment, using implanted, smart sensors on silicon, fabricated in the University's Scottish Microelectronics Centre. IMPACT will use miniaturised, wireless sensor chips the size of a grass seed to monitor the minute-to-minute status of an individual tumour. This will allow RT to be targeted in space and time to damage cancer cells as much as possible. 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 – the cluster of normal cells, molecules, and blood vessels that surrounds the tumour, but is not part of it. The blood supply of a tumour is chaotic and when it develops rapidly, it can outgrow its own oxygen supplies. The oxygen-starved cancer cells that result, while still deadly, resist both RT and chemotherapy. Most frustratingly, the RT-resistant, oxygen-starved, or hypoxic, regions are not static – they change and move in time. However, RT is currently delivered in regular, scheduled sessions to the same volume of tissue containing the tumour, as determined by an accurate snapshot in time from a CT or MRI image. At the same time, advanced RT technology now enables higher doses of X-ray treatment to be aimed selectively at different parts of a cancer. This creates an urgent, unmet clinical priority: to capture in space and time the rapid, highly-localised and transitory changes in hypoxia, pH and other key biomarkers (eg proteins and nucleic acids) that 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. Indirect measures do not capture vital, rapid changes in oxygenation and today's invasive probes are impractical in patients.

The diagram below shows the IMPACT principle. A group of cancer cells (A) is identified for RT treatment. 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. Before treatment, sensor chips will be inserted stereotactically (C) amongst this cluster of cells. The sensor chips (D) will identify the RT-resistant regions (5) and relay this information to the radiotherapist. RT will then be aimed and timed (E) to do maximal damage to the stubborn, RT-resistant cancer cells. IMPACT's sensors will measure not only oxygen levels, but 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. IMPACT will measure their concentration to gather further intelligence on the success of RT in destroying the cancer. IMPACT 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 aims to deliver 'proof of principle' in 2-3 years from now – then they will move the technology rapidly toward the clinic.



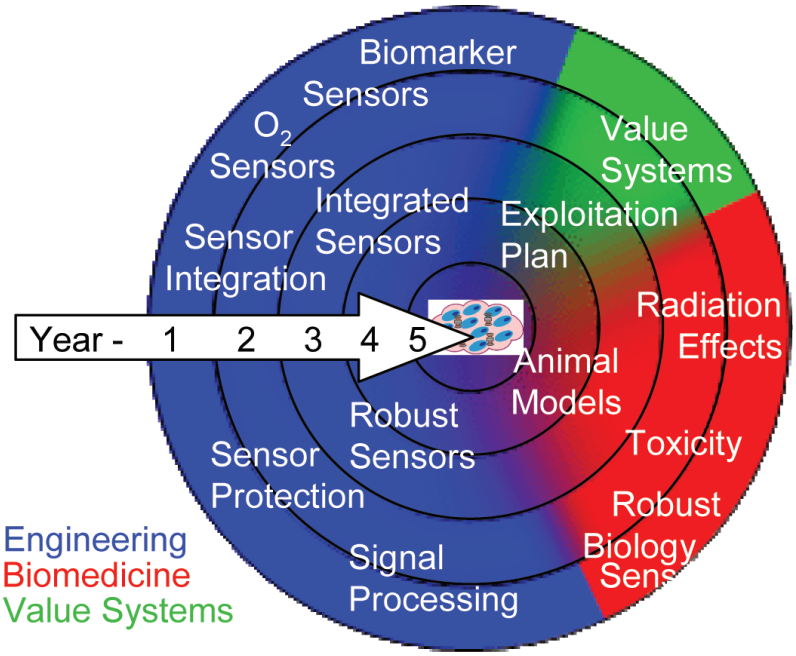
SOME DETAIL – IMPACT'S RESEARCH CHALLENGES

IMPACT must integrate radically new sensors on silicon with the instrumentation, control and communications that they require. The final choice of sensor technologies will depend upon; (a) sensor responses and calibration, (b) the size of the implanted device, (c) techniques to place sensors on standard chips and (d) chip "packaging" technology for long term implantation. Initially, the system will be developed as a set of individual chips. The final system will integrate sensors, instrumentation and communications on a single device.

Biomarkers that are directly implicated in cancer progression, cancer cell death (apoptosis) or necrosis will be targeted, including Caspase-9, transcription factors such as Hypoxia-inducible factors (HIFs) and the nucleic acids (specifically DNA) released by dying cells. The caspases are ideal monitors of apoptosis (cell death). IMPACT's challenge is to detect relevant cancer biomarkers, specifically and sensitively. This approach will, however, be applicable generically to other protein and nucleic acid biomarkers, enabling a suite of specific biomarker sensors to be incorporated readily on chip.

The body's immune system responds to an object implanted over long periods by developing protein plaques or scar tissue to encapsulate it. This may affect sensor performance and may require suppression. We will extend a drug delivery technology developed at the University of Edinburgh to protect sensors from biofouling and expose them to the tumour microenvironment at defined times. Over 200 such elements will be generated per biomarker with ten exposed at a time to allow signal averaging and internal controls.

Radiation damage is also a concern. We have demonstrated that the electronic components of CMOS sensor chips can survive exposure to radiation, if they are powered down during RT – the same tests will be applied to sensor chips.



Initially, in the interests of simplicity, the implanted sensors will be connected to the outside world via wires for power delivery and data transfer. However, this is undesirable due to the problems presented by wires breaking through the skin and the ultimate aim will be to develop an implant which communicates wirelessly and either has power supplied to it by wireless power transfer or has an on-board battery. IMPACT's biosensor and instrumentation designs must take misalignment and misregistration of an implant with its external power and communications into account, additionally requiring low power operation and possible digitisation and compression of hypoxia measurement results to reduce transmission power requirements. It may be necessary to use a combination of inductive communications (across the skin barrier) with ultrasound communications (within the body).

To deliver its technology to patients as rapidly as possible, IMPACT will use a strategic planning or roadmapping technique for the sensor chips to analyse and optimise future value chains (the sequences of activities that a company performs in order to bring a valuable, and therefore profitable, product to the marketplace). This will take account of current and future regulatory developments for implantable biosensors, currently a vibrant and rapidly-changing area in the European regulatory system. IMPACT will also take account of patients' and public understandings and perspectives on acceptability and future use of its technology. Experience from previous research using this approach has shown that decisions taken early in the research process can have profound and unexpected implications for the future development and uptake of a new technology in a public health or commercial context. This approach will enable IMPACT researchers to explore the downstream implications of such decisions and to refine them with future opportunities in mind.

IMPACT TEAM

Engineering (University of Edinburgh & Heriot-Watt University)
Prof Alan Murray; Prof Anthony Walton; Dr Stewart Smith; Dr Brian Flynn and Dr Martin Reekie; (Edinburgh) Prof Steve McLaughlin (Heriot-Watt)

Chemistry (University of Edinburgh)
Prof Mark Bradley and Prof Andy Mount

Veterinary Medicine (University of Edinburgh)
Prof David Argyle

Innogen Institute (University of Edinburgh)
Prof Joyce Tait and Dr Gill Haddow

Molecular & Clinical Medicine, Edinburgh Cancer Research UK Centre
Prof Ian Kunkler

Clinical Research Imaging Centre, Western General Hospital (NHS & University of Edinburgh)
Prof Edwin Van Beek and Dr Duncan McLaren

Oncology Physics, Edinburgh Cancer Research UK Centre
Dr Bill Nailon