BSRC-funded cell biology research at the University of Cardiff is enabling drug discovery at pharmaceuticals company Merck. The research, led by Professor Trevor Dale, identified proteins involved in the ‘Wnt’ signalling pathway in cells, which controls the activity of genes associated with embryo development. By understanding the proteins involved, the researchers were able to work with Merck to identify potential new drugs that inhibit the pathway and which could be used to treat associated diseases, including several cancers.

“The BBSRC grant was central to the establishment of a major drug discovery programme with Merck and in the development of a novel technology for in vitro drug discovery,” says Dale.

The BBSRC funding supported a long-standing collaboration between Cardiff University, the Institute of Cancer Research and Merck. The collaboration also resulted in research that supported the establishment of the spin-out company, Cellesce. The company provides products and services to enable the scale-up and optimisation of drug discovery and regenerative medicine processes.

Cell signalling pathways such as the Wnt pathway are one of the mechanisms by which cells detect and respond to the external environment. They consist of a receptor on the cell surface that, when activated, triggers changes in a pathway or network of proteins that carry the signal to the cell nucleus. Here, the signal results in a change in gene activity, altering the behaviour of the cell. These networks regulate cellular processes and a malfunction, for instance a mutation in a gene encoding one of the proteins in the pathway, can result in diseases such as cancer.

The Wnt signalling pathway plays a vital role in embryo development, including defining the alignment of the body axis, determining how cells specialise as they develop, and controlling cell growth and migration. As a result, mutations in genes involved in the Wnt pathway can lead to uncontrolled cell growth and have been implicated in breast cancer, as well as melanoma, colorectal, prostate and lung cancers.

In previous research supported by Cancer Research UK, Dale and colleagues had generated a ‘reporter’ line of cells that emit a burst of light when the Wnt signalling pathway is activated in the nucleus of the cell. They also knew, from earlier work, that there were up to 250 genes that may be involved with wnt signalling in some capacity.

The research, supported through a BBSRC Industry Partnering Award, enabled Dale and colleagues to screen 18,000 genes to identify those that regulated the activity...
Unravelling cell signalling mechanisms to enable drug discovery

of the Wnt pathway. To do so, they used a technique called RNAi to inhibit the activity of each of the 18,000 genes, reducing the amount of protein produced by that gene present in the cell. If the protein is important in the Wnt signalling pathway, reducing the amount in the cell should inhibit the pathway and prevent the flash of light in the nucleus of the reporter cell line created by Dale. The BBSRC funding also led to the development of a cell-based assay, which was used to test the effects of potential drug molecules on the Wnt pathway.

The RNAi screening identified a number of genes that regulate Wnt signalling. Using that knowledge, together with the cell assay, the researchers could then work with Merck to look for potential drug molecules that inhibited the activity of those genes, and which could be used to inhibit the activity of the wnt pathway as a whole. In total, they found four potential ‘hits’ that could block the growth of tumour cells caused by mutations in the wnt pathway, details of one of which have since been published3.

On-going work with the company is now helping to further develop those hits into useful therapeutics. For instance, Dale and colleagues were awarded a BBSRC CASE studentship with Merck to investigate the interactions between several genes identified during the screening work, which will contribute to the design of anti-cancer drugs.

REFERENCES
2. BB/D00117X/1. Determining the functional order of Wnt signalling components: http://gtr.rcuk.ac.uk/projects/ref=BB/D00117X/1