A step beyond current “one-size-fits-all” cancer treatments

Dr Gillian Smith
PhD Supervisor, School of Medicine, University of Dundee

What is the problem?

Many common cancers, including colorectal (bowel), breast and ovarian cancers are treated with chemotherapy, where the choice of chemotherapy drug(s) is defined by cancer type. Individual cancer patients often respond quite differently to chemotherapy, however, and many patients who initially respond well to treatment become drug “resistant” as their treatment progresses.

The development of resistance is a major cause of cancer death as it is one of the main reasons that chemotherapy stops working.

What are we interested in?

We wanted to find out how cancer cells change when they become resistant, and to do this we compared the levels of candidate proteins which we thought might influence chemotherapy response. We showed that a family of specialised proteins, fibroblast growth factors (FGFs), control how quickly individual cancers grow and how patients respond to treatment. Individual cancers have different amounts of FGF proteins (Figure 1A), and the amount of FGF proteins is increased in drug resistant cells (Figure 1B). When we “knock out” individual FGF proteins in resistant cells, the cells start to respond to chemotherapy (cisplatin) again (Figure 1C). FGF proteins work by binding in a “lock and key” mechanism with specialised FGF receptors (Figure 2) – individual cancers each contain different amounts of more than 20 different FGFs and 4 FGF receptors. We have worked out which FGFs unlock FGF receptors in ovarian cancer cells, and have recently shown that these mechanisms are also important in colorectal and breast cancer.

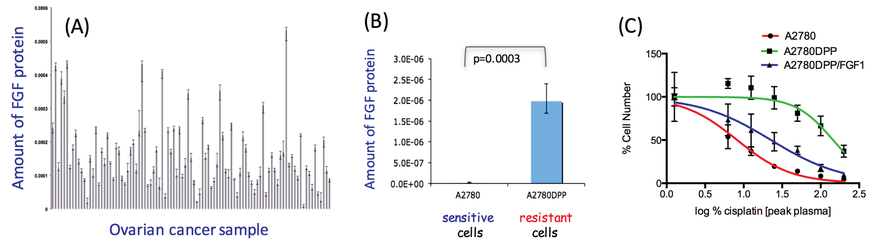


Figure 1 (A) Ovarian cancer tissue samples from different patients have different amounts of FGF proteins. **(B)** FGF proteins are present at higher levels in drug-resistant cells. **(C)** Drug-resistant A2780DPP cells are much less easily killed by the chemotherapy drug cisplatin than drug-sensitive A2780 cells. If we “knock out” FGF proteins in A2780DPP cells (A2780DPP/FGF1), they become much more responsive to chemotherapy.

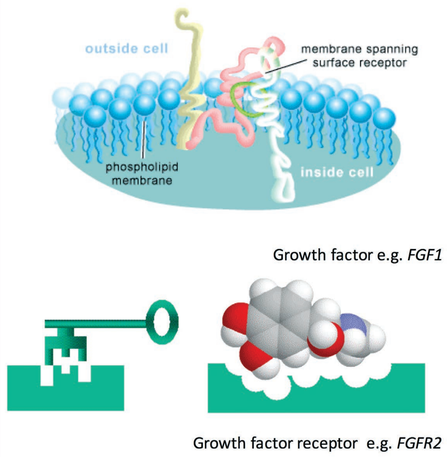
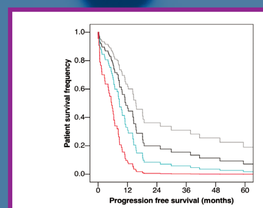


Figure 2 Lock and key mechanisms controlling FGF growth factors

How did we do it?

We used a very sensitive method (qRT-PCR analysis) to compare hundreds of ovarian, colorectal and breast cancers and showed that the amount of each FGF and FGF receptor was very different. We used statistical analysis to show that patients with high FGF expression die more quickly than patients with low expression (Figure 3), and we used cell lines created from sensitive and resistant patients to show that FGF levels are higher in resistant cells. We treated our cell lines (± FGF knockout) with chemotherapy drugs to confirm that the amount of FGF influences whether cells survive or are killed by chemotherapy treatment.



Quartile range of *FGF1* expression (%)	Median survival (months)	Hazard ratio	95% CI
<25	465.5	1	
25-50	334	1.591	0.612-4.133
50-75	205.5	2.434	0.991-5.975
>75	188	5.123	2.015-13.028

Figure 3 “Survival” analysis, showing that the amount of FGF proteins in individual cancers has a big influence on how long cancer patients live – patients with high FGF levels (red) live for the shortest time and vice versa.

What does it mean?

Understanding which FGF locks and keys are most important in common cancers will allow us to understand why some cancers progress more quickly and why some patients respond better to chemotherapy than others. In future, we hope that our research will lead to the development of new, more “personalised” treatments for cancer patients and the identification of new drug targets.

Who are we?

We are a translational team of laboratory scientists and clinicians (oncologists, pathologists and surgeons) based in the Jacqui Wood Cancer Centre, Ninewells Hospital & Medical School, Dundee. We work in collaboration with Dundee Cell Products to create novel reagents to help us work out which FGFs have the most important influence on cancer cell behaviour. I am the supervisor of this PhD Studentship and a Senior Lecturer in the Division of Cancer Research at the University of Dundee.

Dr Gillian Smith began supervising the PhD project entitled *“Specificity of fibroblast growth factor-induced signalling pathways in human tumours – identification of novel therapeutic targets?”* in 2013 and while the Studentship is principally based at the University of Dundee, it is delivered through close work with Dundee Cell Products Ltd.