Project proposal template
Graduate School studentships
March 2015

Project title	Fibroblast growth factor signalling in cancer: with emphasis on cervical and breast cancer
First Supervisor	Professor — Anthony J Walker
Second Supervisor	Dr Athina-Myrto Chioni
School	Life Sciences
Other member of supervisory team (no more than three KU supervisors in total)	Professor Helmout Modjtahedi (KU) Dr Richard P. Grose (Barts Cancer Institute at
Specific requirements beyond 2:1 degree	

Project summary

(max 4,000 characters)

Growth factors are used during development to convey messages that tell cells to divide, survive, migrate and adopt a particular fate. This is particularly true of the Fibroblast growth factors (FGFs), whose signals are critical for the development of many organs. Since FGFs provide powerful growth signals, their signalling pathway is tightly regulated. However, some cancer cells hijack this pathway to gain a growth advantage over normal cells. FGF s and their receptors, FGFR1 & FGFR2, have been implicated in cancer susceptibility and progression (i.e breast, cervical, endometrial, prostate, lung cancer), suggesting that FGF signalling may be co -opted by cancer cells. FGFRs signal from the cell membrane and from endosomal compartments via MAPK, PI3K, PLC-gamma and STATs. However, there is evidence that other tyrosine kinase receptors as well as full-length FGFRs can be targeted to the nucleus.

We previously showed that a C-terminal fragment of FGFR1, traffics to the nucleus and regulates the expression of target genes. We confirmed Granzyme B (GrB) as the protease that mediates cleavage and showed that GrB inhibition blocks specific FGF-dependent effects. We demonstrated that this phenomenon also occurs *in vivo* in invasive breast cancer and have identified a panel of FGFR1-regulated target genes, all of which regulate cell migration likely reflecting an invasive signature (Chioni & Grose 2012). **Thus we described a novel mechanism by which FGF signalling can regulate cancer cell behaviour, and suggest a novel therapeutic target for treatment of invasive breast cancer. We showed that endogenous GrB plays a promigratory role, at least in part through cleaving FGFR1.**This proposed project is a natural progression from our previous studies and it is based on two key findings regarding FGFR signalling is breast cancer and recently in pancreatic cancer (Coleman, Chioni et al., 2014; Chioni et al. 2012):

(I) FGFR1 translocates to the nucleus upon stimulation with its ligand and this is correlated with metastatic cell behaviours both in 2D and 3D cell culture models, as well as in human patients.

(II) We have identified in breast cancer a novel mechanism, whereby FGFR1 is cleaved, by GrB, and the C-terminus portion of FGFR1 then translocates to the nucleus and acts as a transcription factor.

AIMS:

1. Investigate FGF and FGFR expression, subcellular localisation and signalling in cervical cancer cells.
2. Develop an organotypic model (3D model) for cervical cancer building on the organotypic models we previously developed for breast cancer and skin (Chioni & Grose, 2012; 2008) in order to investigate FGF(R) expression and signalling in a more physiological environment.
3. Determine GrB expression in cervical cancer cells and whether the FGFR gets cleaved in a similar manner as in breast cancer cells.
4. Investigate expression of other tyrosine kinase receptors such as EGFR in cervical and breast cancer and determine possible cross-talk or any correlation with FGFR signalling.

The potential PhD student will become proficient in a wide range of cellular and molecular techniques (e.g. Western blots, PCR, overexpression of FGFR(s), RNAi, functional studies such as proliferation, migration, invasion, organotypic modelling) that will be used to answer important scientific questions relating to cell signalling and cancer. The supervisory team comprises experienced scientists that are all experts in the field of cell signalling and cancer biology. Prof Walker is expert on cell signalling pathways and Prof Modjtahedi has deep knowledge on the biological and clinical significance of tyrosine kinase receptors in cancer biology. Dr Chioni's previous experience in the field of FGF signalling in cancer, as well as her familiarity with the techniques required, will drive this project. The project will also be enhanced by collaboration with external supervisor Dr Grose from The Barts Cancer Institute QMUL who is a leading scientist in the field.