**Erasmus MC / EUR CSC PhD 2014 Project Description**

**School/Department:** Molecular Medicine Research School, Department of Neurology

**Project Title:** **Identification of Mutation-Specific EGFR inhibitors**

**Abstract:**

Introduction: **The epidermal growth factor receptor (*EGFR*) gene is a key oncogene that is mutated in many different cancer types**. Although these mutations result in a constitutively activated isoform of the receptor, clinical benefit of EGFR-inhibition has thusfar been limited to a subset of pulmonary adenocarcinomas with activating mutations in the kinase domain. Interestingly, a detailed examination reveals **that each tumor type has its own specific type of genetic change**. For example, approximately 1/3 of all glioblastomas (GBMs) have an in-frame deletion of exons 2-7 (*EGFRvIII*) whereas common mutations in pulmonary adenocarcinomas (5-10%) are small activating deletions/point mutations in exons 19 and 21. Although all mutations are activating, it remains unclear why specific mutations are restricted to one tumor type only. One explanation for this is that each mutation has its own unique properties. The implication of this hypothesis is that **each mutation requires its own specific inhibitor**. Indeed, where gefitinib and erlotinib act on kinase domain mutations, lapatinib is effective on extracellular domain mutations (but does not reach sufficiently high concentrations in the tumor to be effective). The goal of this project therefore is to identify new drugs and drug targets that act on specific mutations in EGFR.

Preliminary results: We performed a comparison between three EGFR variants (*EGFR*, *EGFRvIII* and *EGFRL858R*) and demonstrate that each mutation has a unique set of binding partners, induce expression of a different set of genes and activate different signal transduction pathways. As a result, each mutation has different effects on proliferation and migration. Our preliminary results thus demonstrate that different mutations in *EGFR* have different and tumor type specific consequences that form good leads to develop novel therapies. Primary celllines with different mutations in EGFR have been established (in collaboration with Dr. Kerrie McDonald, UNSW, Australia).

Aim:. To identify new drugs and drug targets that act on glioma-specific mutations in EGFR we will:

1. Analyze biochemical and molecular pathways induced by different *EGFR* mutations.
2. Determine if we can specifically target the different EGFR mutations.
3. Determine if we can target the pathways activated by different EGFR mutations.

Plan of investigation:

i) We will first generate constructs with the most frequent mutations in EGFR. For all constructs we will analyze binding partners (Mass-spectrometry) and determine pathway activation (phosphoprotein arrays, RPPA). Functional effects of the interaction will be determined using RNAi/inhibitors.

ii) We will determine the sensitivity of the various mutations to EGFR inhibitors on phosphoprotein arrays and determine the sensitivity on primary cultured cell lines.

iii) We will determine the sensitivity of the different mutations to inhibitors on stably transfected and primary cultured cell lines.

**Requirements of candidate**: Background: The candidate will have a strong interest in cancer biology and preferably has a background in molecular and cell biology.

Master degree: Yes

IELTS Grade: 7.0 *(minimal 6.0 per component)*

*Or* TOEFL: *100 (minimal 20 per component)*

**supervisor information:** Dr. Pim French

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**Selected references (out of >50 peer reviewed manuscripts)**

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13. **French PJ**, Swagemakers SM, Nagel JH, Kouwenhoven MC, Brouwer E, van der Spek P, Luider TM, Kros JM, van den Bent MJ, Sillevis Smitt PA. Gene expression profiles associated with treatment response in oligodendrogliomas. Cancer Res 2005;65:11335-44.

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