ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	**Department of Neurology**
Project Title:	Enzymatic detection of kinases in brain tumor tissue
Abstract:	Kinases are proteins that are involved in the function of various pathways and protein cascades in cells. In the oncogenesis and progression of brain tumors, kinases play a prominent role. Extensive genomics analyses (including RNAseq) have clearly demonstrated that in glioma kinases such as EGFR can be amplified but also contain many different mutations and deletions (Brennan et al. 2013). We recently developed a novel technique to determine kinase activity. In short, we synthesized specific peptide substrate molecules that can be converted by an individual kinase and measured by mass spectrometry (MS). This MS technology allows detection of kinase activity in primary glioma cell cultures. Further, we were able to quantify specific kinase activity using stable-isotope labelled substrate and product molecules. However, primary cell cultures are a model for glioma and might not reflect the actual situation in the tumor tissue. In this project we like to address the following research questions 1) can we detect kinase activity in frozen pure kinases as processed in the situation of frozen tissue 2) can we detect kinases in fresh frozen glioma tissue 3) does the glioma primary cell culture model reflect the kinase activity in the original glioma tissue. 4) can we correlate the kinase activity profile of various kinases including EGFR with RNA microarray and next generation sequencing data, protein identification and phosphosites of kinases of a series of glioma tissues and primary glioma cell cultures. 5) Can we understand that some drugs affecting kinases are not working properly in glioma because of aberrant kinase activity, kinase abundance, specific post-translational phosphosite modifications, mutations or combinations thereof. The project is embedded in an awarded STW grant (2013) titled: Defining Kinase Activity for Personalized Cancer Treatment: Development of Next Generation Multiplex Mass-Spectrometry based Kinome Profiling. (STW= a technology innovation support of the Dutch government) For review: Zahonero C and Sanchez-Gomez P, EGFR-dependent mechanisms in glioblastoma: towards a better

	therapeutic strategy. Cell Mol Life Sci. 2014 [Epub ahead of print]
Requirements of candidate:	Master degree: Yes Background: The candidate ought to be a motivated student with interest in biology, technology and bioinformatics. The candidate (him/her) ought to be able to write in scientific English language. It is highly appreciated if the candidate can speak the English language well. IELTS Grade: 7.0 (minimal 6.0 per component) or TOEFL: 100 (minimal 20 per component)
Supervisor information:	Prof. dr. Peter Sillevis Smitt (promotor) / Dr. Theo Luider (co-promotor) Email addresses : p.sillevissmitt@erasmusmc.nl t.luider@erasmusmc.nl Personal website Recent publication list, preferably last 3-5 years (1-2 pages)[1-62] 1. Stingl, C.; Soderquist, M.; Karlsson, O.; Boren, M.; Luider, T. M., Uncovering effects of ex-vivo protease activity during proteomics and peptidomics sample extraction in rat brain tissue by oxygen-18 labelling. *J Proteome Res* **2014**. 2. Rodriguez-Blanco, G.; Burgers, P. C.; Dekker, L. J.; Ijzermans, J. J.; Wildhagen, M. F.; Schenk-Braat, E. A.; Bangma, C. H.; Jenster, G.; Luider, T. M., Serum levels of arachidonic acid metabolites change during prostate cancer progression. *Prostate* **2014,** 74, (6), 618-27. 3. Liu, X.; Dekker, L. J.; Wu, S.; Vanduijn, M. M.; Luider, T. M.; Tolic, N.; Kou, Q.; Dvorkin, M.; Alexandrova, S.; Vyatkina, K.; Pasa-Tolic, L.; Pevzner, P. A., De novo protein sequencing by combining top-down and bottom-up tandem mass spectra. *J Proteome Res* **2014,** 13, (7), 3241-8. 4. Liu, N. Q.; Stingl, C.; Look, M. P.; Smid, M.; Braakman, R. B.; De Marchi, T.; Sieuwerts, A. M.; Span, P. N.; Sweep, F. C.; Linderholm, B. K.; Mangia, A.; Paradiso, A.; Dirix, L. Y.; Van Laere, S. J.; Luider, T. M.; Martens, J. W.; Foekens, J. A.; Umar, A., Comparative proteome analysis revealing an 11-protein signature for aggressive triple-negative breast cancer. *J Natl Cancer Inst* **2014,** 106, (2), djt376.

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