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Geneeskunde & Farmacie

GF

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PhD in Medical Sciences
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Openbare verdediging van/*Public defence of*

Gang CHEN

Voor het behalen van de academische graad van
'**DOCTOR IN DE MEDISCHE WETENSCHAPPEN**'
To obtain the academic degree of
'***DOCTOR IN MEDICAL SCIENCES***'

New Strategies of Targeting the Epidermal Growth Factor Receptor in Non-Small Cell Lung Cancer Cells to Overcome Resistance to Tyrosine Kinase Inhibitors

Promotor: Prof. J. De Grève
Co-promotor: Prof. P. Kronenberger, dr. E. Teugels

Wednesday 10 October 2012
Auditorium Brouwer, 17:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

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Vrije Universiteit Brussel

Situering van het proefschrift/*Summary of the dissertation*

Although the management of non-small cell lung cancer (NSCLC) has been transformed by the observation that NSCLC patients harboring mutations in epidermal growth factor receptor (EGFR) are uniquely sensitive to EGFR tyrosine kinase inhibitors (TKIs), in these patients, acquired resistance to EGFR TKIs develops after a median of 10 to 14 months. Several possible mechanisms for acquired resistance have been identified, the most common being the development of an EGFR T790M gatekeeper mutation in more than 50% of cases. The thesis by Gang Chen studies different strategies to overcome acquired resistance by targeting the EGFR pathway. EGFR-specific siRNAs were found to strongly inhibit cell growth and induce cell apoptosis in all NSCLC cell lines studied, and the cells showing weak response to TKIs, such as the H1975 cell line containing the T790M resistance mutation, were found to be responsive to EGFR-specific-siRNAs and T790M-specific-siRNAs. Knockdown of EGFR by siRNAs further decreases the growth of NSCLC cells that are treated with TKIs or cetuximab alone. Furthermore, the combination of EGFR siRNAs plus c-MET siRNAs enhanced growth inhibition, apoptosis induction and inhibition of downstream signaling in EGFR TKIs resistant H358, H1650 and H1975 cells. EGFR TKIs or cetuximab plus c-MET inhibitor su11274 were also consistently superior to either agent alone. The strongest biological effect was observed when afatinib, an irreversible EGFR/HER2 blocker was combined with su11274, which had a synergistic effect in the cell line H1975. Finally, one of the EGFR targeted microRNAs, miR-146a could suppress cell growth, induce apoptosis, inhibit migration and inhibit EGFR downstream signaling in NSCLC cell lines. MiR-146a also enhanced the cell proliferation inhibitory effect of drugs targeting EGFR, including TKIs (gefitinib, erlotinib, and afatinib) and monoclonal antibody (cetuximab). Additionally, in clinical formalin fixed paraffin embedded (FFPE) samples, miR-146a expression was related to TNM stages, metastatic status and patient survival. The findings in this thesis thereby offer preclinical proof of principle for combined treatment strategy for NSCLC, especially for patients in whom current EGFR-targeted treatments fail due to the presence of the T790M-EGFR-mutation.

Curriculum Vitae

Gang Chen obtained his MD diploma at the Guilin Medial College in Guangxi Province, China (July, 2000). He became a lecturer of Pathology in Guilin Medical College and a resident in Pathology at the Affiliated Hospital of Guilin Medical College (July, 2000-July, 2002). He obtained the degree of Master in Pathology on Biomarkers of Hepatocellular Carcinoma at Guangxi Medical University, China (July, 2005). At the end of 2006, he initiated his PhD research on Molecular Cancer Research in Lung Cancer, in the Laboratory of Medical and Molecular Oncology (LMMO), Medical Oncology Department, at the Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel (VUB). His research resulted in publications in peer-reviewed life science journals. He has also been invited to present his research data in national and international congresses.