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Geneeskunde & Farmacie

GF

PhD in Medical Sciences
2015-2016

INVITATION to the Public defence of

Ijeoma UMELO

To obtain the academic degree of **'DOCTOR IN MEDICAL SCIENCES'**

The HER family network in non-small cell lung cancer: therapies and mechanisms of resistance

Thursday 17 September 2015
Auditorium **Brouwer**, 17:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

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Summary of the dissertation

Lung cancer is the leading cause of cancer death world-wide. The most characterized sub-type, non-small cell lung cancer (NSCLC), accounts for 85% of cases with a majority of patients presenting with advanced stage disease. The elevated mortality of lung cancer is principally due to early metastatic disease, late diagnosis and resistance to currently available treatment approaches. In the past decade, the human epidermal growth factor receptor (HER) family, (EGFR, HER2, HER3 and HER4), have come to the forefront given their strong correlation with lung cancer pathogenesis. This dissertation aimed to investigate the functional relevance of known and novel NSCLC-derived HER family mutations and examine methods to circumvent both intrinsic and acquired resistance to classical and targeted therapies in advanced NSCLC.

First, we elucidate the functional and therapeutic relevance of the resistance-conferring EGFR ^{T790M} mutation arising in *cis* or *trans* to primary EGFR mutations.

Second, we demonstrate a correlation between EGFR status and invasive capacity. We also examine possible therapeutic targets that can abrogate invasive growth.

Third, we demonstrate that the major NSCLC-derived HER2 mutations can be effectively suppressed with specific HER-targeted combination therapies.

Fourth, we elucidate the functional and therapeutic relevance of a novel NSCLC-derived V855A mutation, identified in kinase-impaired HER3 during a phase II clinical study.

Finally, we demonstrate that mutant KRAS isoforms resistant to EGFR targeted therapy can be classified into two distinct groups. We further demonstrate that HER-targeted combined therapy promotes *in vitro* and *in vivo* efficacy in a specific subset.

Taken together, our results further clarify some aspects of HER therapeutic targeting and provide a basis for improved therapeutic strategies that can overcome resistance.

Curriculum Vitae

Ijeoma Adaku Umelo was born in Lagos, Nigeria. In 2002, she obtained a bachelor degree in Chemistry from McGill University, Montréal, Canada. After working briefly in Maryland, USA in the field of health care, she moved to Belgium in 2005 where she began her master in Medical and Pharmaceutical Research at the Vrije Universiteit Brussel (VUB). Her master thesis entitled 'Functional analysis of EGFR mutations in non-small cell lung cancer' was conducted at the laboratory of medical and molecular oncology (LMMO) under the guidance of Prof. Dr. Jacques De Grève and Dr. Erik Teugels. In 2007, she obtained her master degree, earning the best result of her graduating class. Her research interest in personalized and targeted lung cancer therapy resulted in a PhD project at LMMO for which she was awarded in 2008 a four year PhD fellowship from the Onderzoeksraad VUB. Her research findings and collaborative efforts have been published in several international peer-reviewed journals, and communicated as both oral and poster presentations in both national and international conferences. In addition, she has supervised two master's theses and several short-term trainees.