

6th International Conference on

Bioinformatics & Systems Biology

August 22-23, 2016 Philadelphia, USA

An integrative model to improve anemia treatment in non-small cell lung carcinoma patients

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Chemotherapy-associated anemia is a common complication affecting 40% of all cancer patients. It is particularly prevalent in lung carcinoma, with an incidence of 50-70% during disease development and reaching $\leq 90\%$ at advanced stages. The anemia reduces the therapeutic response and the quality of patients' life. Erythropoiesis Stimulating Agents (ESAs) have been widely used to re-establish normal levels of erythrocytes. However, several clinical trials reported higher mortality risk in ESA treatment and low levels of erythropoietin receptor (EpoR) protein expression has been found in tumor cell lines, rising concerns on EpoR activation in tumor context by ESA treatments. To quantitatively analyze the dynamics of interaction of the ligand erythropoietin (Epo) and the EpoR in the tumor and hematopoietic context, we combined mathematical modeling with quantitative data from pharmacokinetic and pharmacodynamic experiments of ESAs in human subjects, ESAs depletion in human erythroid progenitors and Non-Small Cell Lung Carcinoma (NSCLC) cell lines and the activation of signal transduction through the EpoR by mass spectrometry. The experimental data was used to establish an integrative mathematical model utilizing coupled ordinary differential equations (ODE) that links the cellular scale with the body scale. The ODE model was able to describe the dynamic interaction of all ESAs at molecular, cellular and systemic level in the human body. With this approach, we could estimate the binding properties of all tested ESAs and predict personalized optimal dosage protocols for each ESA to activate the EpoR in the hematopoietic context but not in the tumor context.

Biography

Ursula Klingmüller has completed her PhD from Heidelberg University, Germany and Post-doctoral studies at Harvard Medical School in Boston and Whitehead Institute for Biomedical Research in Cambridge, MA, USA. She is the Head of the division "Systems Biology of Signal Transduction" at the German Cancer Research Center (DKFZ) in Heidelberg, Germany and Professor at the University of Heidelberg. She has published more than 90 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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