Immanuel Freedman, Transl Med 2013, 3:2
http://dx.doi.org/10.4172/2161-1025.S1.008

OMICS Group Conferences
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2nd International Conference on
Translational & Personalized Medicine

August 05-07, 2013 Holiday Inn Chicago-North Shore, IL, USA

Translational pharmacometric models of anti-cancer antibodies

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Translational pharmacometric models that address safety and efficacy may accelerate development of anti-cancer antibodies by refining strategic and tactical decisions from target selection to Phase III. A case study for a hypothetical mAb illustrates target selection based on a computational biology model of a PI3K signaling pathway and its cross-talk with a MAPK pathway. Selecting HER-3 as target, the model suggests a PTEN protein may be a key determinant of pertuzumab resistance in ovarian cancers over-expressing HER-2 and expressing HER-3. Hypothetical wild-type and defucosylated variants of a mAb directed against HER-3 may demonstrate blocking of ligand binding and HER-2/HER-3 heterodimerization together with ADCC activity against a cancer cell line *in vitro* with reduction of [pHER3]/[HER3] and [pAkt]/[Akt] biomarkers. A macroscopic model enables rational candidate selection by relating *in vitro* activity to *in vivo* viable tumor cell count and quantifiable resistance in SCID and transgenic hFcγR3a mice bearing xenograft. Translating the *in vivo* model to human patient enables an adaptive First in Man trial design, with predicted tumor size and ORR endpoints based on a modified RECIST 1.1 criterion for viable tumor cells and tumoral tissue detected on an arterial phase CT scan. This translation may require population pharmacokinetic and dose-safety models for the mAb in monkey together with measured human donor target levels and epidemiological rates of observed human tumor growth. A drug-independent epidemiological model may then translate the Phase I or Phase II tumor size endpoint to an OS Phase III endpoint, with ECOG functional score as potential covariate.

Biography

Immanuel Freedman is a Manager, Clinical Pharmacology at GlaxoSmithKline. Educated at Durham, England in Physics, he is qualified as Chartered Physicist, Senior Member of The Institute of Electrical and Electronic Engineers and Registered Patent Agent. He focuses on Translational Pharmacometric Modeling and Imaging across therapeutic areas, indications and phases from pre-clinical to post-marketing.

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