Dynamic Bioluminescence Imaging: Development of a Physiological Pharmacokinetic Model of Tumor Metabolism

P.R. Territo[1]*, H.E. Shannon[2], K.J. Freise[5], A.A. Riley[1], B.P. McCarthy[1], B.J. Bailey[2,3], S. Cai[2,3], W. Cai[2,3], T.L. Sinn[2,3], H. Wang[2,3], H. Hanenberg[2,4], K.E. Pollok[2,3], and G.D. Hutchins[1]

[1]Indiana University, School of Medicine, Department of Radiology and Imaging Sciences

[2]Indiana University, School of Medicine, Wells Cancer Center

[3]Indiana University, School of Medicine, Pediatrics

[4]Indiana University, School of Medicine, Molecular Genetics

[5]Nexcyon Pharmaceuticals Inc

Abstract

Bioluminescence (BLI) is a technology which has been studied extensively across multiple genera for more than 90 years. Over this period, BLI has emerged as a powerful noninvasive tool to study tumor localization, growth, and response to therapy due to the relatively recent technological advancements in instrumentation and molecular biology. This technology takes advantage of molecular transfection of the luciferase (LUC) gene from the North American firefly, *Photinus pyralis*, into human cancer cells, which are then implanted (ectopic or orthotopic) in mice. Oxidation of the exogenously administered substrate D-luciferin by the LUC gene product results in emission of green-yellow photons which are then evaluated in the context of tumor growth and development. Despite the more than 30 years of characterization, there exists a fundamental gap in our knowledge of the underlying PK/PD processes which are at the heart of nearly all BLI interpretation, and has lead to a dogmatic adherence in the literature to numerical methods which are at best simple corollaries of tumor metabolic rate. In an attempt to fill this void, this paper will present a new PK/PD model which takes advantage of the temporal nature of both substrate transport and light evolution. In addition, we will compare these results to traditional non-model based analyses and show how they differ. Lastly we will present OATS (One at A Time) Parameter Sensitivity and Monte Carlo Noise Analysis to characterize the numerical stability and sensitivity of this new model.