Animals, Humans, and the Continuity of Evidence: A Study of Clinical Translation

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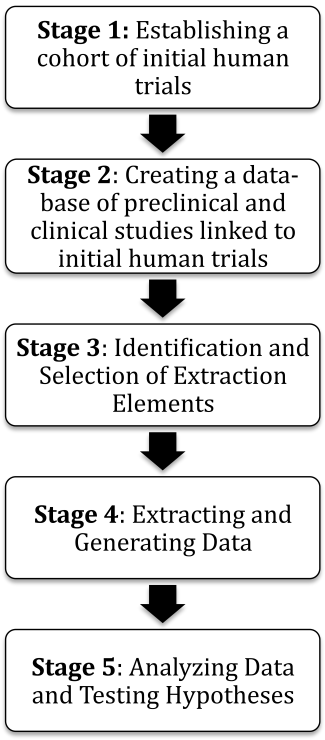
Lay Abstract:
In the last two decades, researchers have made enormous progress in understanding the causes of human disease. Yet many important discoveries have not yet had an impact on the practice of medicine. This grant aims to understand some of the reasons why therapies that show promise in animals never make it to the clinic. We believe one of the reasons is that animal studies are often not as well designed as they should be. This grant will look at a large group of animal and human studies to see whether this is the case. Our study will further allow us to see whether certain research practices might improve chances that a new drug will have a clinical impact, and whether patients benefit or are harmed by participating in first in human drug studies.

Description:
The present study will examine these questions empirically by performing a systematic analysis of experimental practices and outcomes in studies leading toward clinical translation. Our primary goal is to provide a quantitative description of the degree to which preclinical studies address various threats to valid clinical inference. Our secondary goal is to determine whether addressing certain threats predicts successful clinical translation.

Our specific strategy, depicted in the graphic below, is to identify a large cohort of early phase trials of new drugs or biologics. We will next track down preclinical studies supporting these initial studies, as well as subsequent, later stage clinical studies. Preclinical study outcomes will be recorded, as will be practices along three key axes: internal validity, construct validity, external validity. In the final stages of the grant, we will attempt to relate validity practices in preclinical studies to outcomes in clinical studies.



Our cohort will include a sample of ~200 initial human studies of new, unlicensed agents, 2000-2005, inclusive

We will identify all available preclinical studies that correspond with each initial human trial, and clinical studies that follow them

We will develop extraction parameters for study characteristics, validity, and outcomes

Studies identified in stages 1 and 2 will be extracted and elements entered into a database

Frequency of practices reducing threats to validity will be measured, and hypotheses about relationship between methods and outcomes will be tested

Selected Publications from team members supporting grant
(* = team member, † = collaborator)

Kimmelman J*, London AJ*. Predicting Harms and Benefits in Translational Trials: Ethics, Evidence, and Uncertainty. *PLoS Medicine* 2011 (in press)

London AJ*, Kimmelman J*, Emborg ME†. Beyond Protection vs. Inclusion in Trials of Innovative Therapies. *Science* 2010; 328: 829-30.

Hackam DG*, Redelmeier DA. Translation of Research Evidence from Animals to Humans. *JAMA* 2006;296: 1731-2.

Lee DS, Nguyen QT, Lapointe N, Austin PC, Ohlsson A, Tu JV, Stewart DJ*, Rouleau JL. Meta-analysis of the effects of endothelin receptor blockade on survival in experimental heart failure. *J Card Fail* 2003; 9: 368-74.

Marshall JC*, Deitch E, Moldawer LL, Opal S, Redl H, van der Poll T. Preclinical models of shock and sepsis: what can they tell us? *Shock*. 2005; 24 Suppl 1:1-6 .

Rice AS, Cimino-Brown D, Eisenach JC, Kontinen VK, Lacroix-Fralish ML, Machin I; Preclinical Pain Consortium, Mogil JS†, Stöhr T. Animal models and the prediction of efficacy in clinical trials of analgesic drugs: a critical appraisal and call for uniform reporting standards. *Pain* 2008;139(2):243-7.