Enhancing Natural Product Clinical Trials

A workshop on development of criteria for the prioritization of critical research needs for successfully moving natural product (NP) research to optimally informative clinical trials

National Institutes of Health (NIH) campus, September 13 & 14, 2018

Purpose

To enhance return on investment from NP clinical research by bringing together multi-disciplinary experts (NP chemistry, nutrition, clinical trials, cell biology, health economics, etc.) for a structured discussion of (1) good practices and priorities in rigorously assessing the foundational data needed to optimize the translation of NP research to public health outcomes and (2) related knowledge (information) gaps.

Draft Agenda

Day 1			
Time	**Session**	**Talk Topics (speaker)**	**Speakers**
8:30 – 9:00 am	NP translational research: Setting the stage	• Outline and background for the workshop (BCS) • Traditional versus modern use: Implications for translational research (SC) • Need to optimize knowledge gain through rigorous planning for clinical research (CH) • Workshop plans (AJK)	• Barbara C. Sorkin, Office of Dietary Supplements (ODS), NIH • Steve Casper, Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA) • Craig Hopp, National Center for Complementary and Integrative Health (NCCIH), NIH • Adam J. Kuszak, ODS, NIH
9:00 – 10:30 am	The NP intervention: Translatability of assays for bioactives Session chair: Barbara C. Sorkin, ODS, NIH	• Enhancing translational potential of *in vitro* studies: Organoid cultures (HT) • Microphysiological systems/tissues-on-a-chip, *in vivo* metabolites (DLT) • *In vitro* to *in vivo* extrapolation (NS) • Pitfalls of *in vitro* assays, concentrations, and controls (MW)	• Hervé Tiriac, Cold Spring Harbor • D. Lansing Taylor, University of Pittsburgh • Nisha Sipes, National Institute of Environmental Health Sciences (NIEHS), NIH • Mike Walters, University of Minnesota
10:30 – 10:45 am	BREAK		

10:45 am – 12:15 pm	The NP intervention: Determining the critical characteristics for reproducibility Session Chair: Craig Hopp, NCCIH	• Devil's in the details (of NP chemistry): (Stereo-)isomers make a difference (KS) • What is the role of host metabolism in generating bioactivity? Context and hysteretic effects (MF) • Approaches to non-target-ligand mechanisms of action (MJ) • Generating strong causal, molecular mechanism hypotheses for complex NP mixtures (JM)	• Ken Setchell, Cincinnati Children's Hospital Medical Center • Mario Ferruzzi, North Carolina State University • Mahtab Jafari, University of California, Irvine • John MacMillan, University of California, Santa Cruz
12:15 – 12:35 pm	Panel 1: Critical preliminary data for NP selection and specifications Panel Chair: Guido Pauli, University of Illinois at Chicago (UIC)	• What preliminary data are most critical for the selection of (specifications for) the product(s) and control(s) to be tested? • What are optimal approaches to controlling or reporting other variables that may modulate bioactivity, ranging from intra- and inter-NP constituent interactions through history and timing? • To what extent does this depend on the specifics of each research question? • What are critical controls for preliminary data?	Casper, Tiriac, Sipes, Taylor, Walters, Setchell, Ferruzzi, Jafari, MacMillan
12:35 – 1:20 pm	LUNCH		
1:20 – 2:50 pm	Optimizing the foundations for translational NP research: Preclinical models Session Chair: Harold Seifried, National Cancer Institute, NIH	• Authentication, sex, strain differences in preclinical models, consideration of timing, duration of exposure, background/baseline diet, bedding (JS) • Mice are not miniature humans; approaches to enhance translational potential (JP) • Dimensions of model variability and experimental design issues (KPC)	• Jacqueline Stephens, Louisiana State University (LSU)-Pennington Biomedical Research Center • Jeffrey Paul, Drexel College of Medicine • Kathleen Pritchett-Corning, Harvard University
2:50 – 3:10 pm	BREAK		

3:10 – 4:40 pm	Lost in translation: Important individual (and other) differences Session Chair: Giovanna Zappala, National Institute on Aging, NIH	• Application of evidence-based in silico modeling to assist understanding of differences between models and clinical results (SQ) • Effects of individual differences, including sex, on outcomes (RB) • Genetic/biochemical differences: Importance of understanding molecular mechanisms to understanding interpersonal outcome variation (SC) • Clinical trials in an older population (MP)	• Sara Quinney, Indiana University • Ric Bushman, University of Pennsylvania • Floyd "Ski" Chilton, Wake Forest University • Marco Pahor, University of Florida, Gainesville
4:40 – 5:15 pm	Panel 2: Prioritizing clinical trials based on the preliminary data Panel Chair: Freddie Ann Hoffman, Heterogeneity, LLC	What data are sufficient? What is optimal? Are all relevant data equally salient? If not, what types of data are most critical versus less likely to support translation?	Stephens, Pritchett-Corning, Quinney, Bushman, Chilton, Pahor
Day 2			
8:30 – 9:45 am	Optimizing the foundations for translational NP research: Assessing prior research Session Chair: Laura Lee Johnson, FDA	• Placebo effects, importance of masking and appropriate placebo (BB) • Analyzing the strengths/weaknesses/human health relevance of preliminary data to optimally utilize in vitro, preclinical, and clinical research and epidemiology in developing clinical trials (MK) • Rigorous hypothesis testing, P-curve for evaluating evidence (DL)	• Bruce Barrett, University of Wisconsin-Madison • Mairead Kiely, University College, Cork • Daniel Lakens, Eindhoven University of Technology, Netherlands
9:45 – 10:00 am	BREAK		
10:00 – 11:00 am	General strategies for optimizing NP translational research design and yield Session Chair: Greg Bloss, National Institute on Alcohol Abuse and Alcoholism, NIH	• Costs of flawed foundational data (LF) • Modeling clinical trial outcomes to optimize design (BT) • Go/no-go decision points, adaptive trial design (CC) • Value of information and clinical trial decision-making (DM)	• Leonard Freedman, Global Biological Standards Institute (GBSI) • Bruce Tidor, Massachusetts Institute of Technology (MIT) (tentative) • Chris Coffey, University of Iowa • David O. Meltzer, University of Chicago

11:00 am – 12:00 pm	Final panel discussion: Good practices in rigor and prioritization for translational NP research Panel Chair: Naomi Fukagawa, Agricultural Research Service, U.S. Department of Agriculture		• All speakers