BIOGRAPHICAL SKETCH

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NAME: Kagan, Leonid

eRA COMMONS USER NAME (credential, e.g., agency login): KAGANL

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Hebrew University, Jerusalem	BS	06/2000	Pharmacy
Hebrew University, Jerusalem	MS	08/2004	Clinical Pharmacy
Hebrew University, Jerusalem	PHD	04/2009	Pharmaceutics
University at Buffalo, SUNY, Buffalo, NY	Postdoctoral Fellow	12/2010	Pharmaceutics and Pharmacokinetics

A. Personal Statement

I am an Associate Professor in the Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey. My research interests are focused on the investigation of interactions between biological systems and therapeutic agents, with an emphasis on analgesics, antiinfectives and anticancer biotherapeutics. I have been trained in clinical pharmacy, pharmaceutics, drug delivery, pharmacokinetics, pharmacodynamics, and computer modeling and have extensive experience in designing, conducting, and analyzing preclinical and clinical drug therapy studies. I strongly believe that translational mathematical modeling and simulation can be effectively coupled with meaningful experimental systems for understanding mechanisms of these interactions and for optimization of pharmacotherapy in special patient populations. Recently, we have developed and successfully utilized complex physiologically- and mechanism-based mathematical models for predicting pharmacokinetics and pharmacodynamics of biotherapeutics and small-molecule drugs across multiple animal species and in humans.

Ongoing and recently completed projects that I would like to highlight include:

NIH, 1R01AI137080-01A1(PI: Heysell) 09/24/2018-08/31/2023
NIH/NIAID
Urine Colorimetry for Tuberculosis Pharmacokinetics Evaluation in Children and Adults
The goal is to develop approaches for therapeutic drug monitoring in tuberculosis
Role: Co-Investigator

NIH, 1R01GM124046-01A1 (PI: Kagan) 2018/07/01-2023/06/30
Mechanisms of obesity-induced changes in drug pharmacokinetics.
The goal is to optimize dosing in obese patient population for small molecule drugs and protein therapeutics. Preclinical studies combined with PBPK modeling will be validated using clinical studies.

NIH, 1R01DK131214-01 (PI: Brunetti) 2022/02/01- 2027/01/31
Mechanistic evaluation of melatonin as a protectant against antibiotic associated kidney injury.
The goal is to identify the mechanisms of benefit melatonin confers on kidney health and to investigate this natural product as a kidney protectant.
Role: Co-Investigator

NIH, 1R01NS104500-01 (PI: Haroutounian) 2018/02/15-2024/01/31
5-HT3 receptor antagonists for neuropathic pain.

The major goals of this project are to determine the CNS disposition of 5-HT3R antagonists and its dependence on efflux transporters in a preclinical model; to determine the role of Pgp efflux transporter in human CNS disposition of ondansetron; and to determine the effect of adequately CNS-penetrating ondansetron in patients with neuropathic pain.
Role: Co-Investigator

1R01GM135258-01A1 (PI: Guo) 06/01/2020– 05/31/2024
NIH/NIGMS
Gut-liver crosstalk by FGF15/19 in regulating xenobiotic nuclear receptor activation
The goal is to investigate effect of FGF15/19 on pharmacokinetics of prove drugs
Role: Co-Investigator

Citations:

1. Rao PS, Moore CC, Mbonde A, Nuwagira E, Orikiriza P, Nyehangane D, Al-Shaer MH, Peloquin CA, Gratz J, Pholwat S, Arinaitwe R, Boum Y, Mwanga-Amumpaire J, Houpt ER, **Kagan L**, **Heysell SK**, Muzoora C. Population pharmacokinetics and significant under-dosing of anti-tuberculosis medications in people with HIV and critical illness. *Antibiotics* (Basel) 2021; 10(6):739. PMID: 34207312.
2. Zentner I, Back HM, **Kagan L**, Nagajyothi J, Subbian S, Pasipanodya J, Srivastava S, Tawanda Gumbo T, Bisson GP, and Vinnard C. Redox imbalance and oxidative DNA damage during isoniazid treatment of HIV-associated tuberculosis: A clinical and translational pharmacokinetic study. *Frontiers in Pharmacology* 2020; 11:1103. PMID: 32848735.
3. Mezochow A, Thakur K, Zentner I, Subbian S, **Kagan L**, Vinnard C. Attainment of target rifampin concentrations in cerebrospinal fluid during treatment of tuberculosis meningitis. *International Journal of Infectious Diseases* 2019; 84:15-21. PMID: 31051278.
4. **Narayanan N**, Adams CD, Kubiak DW, **Kagan L**, Brunetti L. Evaluation of treatment options for methicillin resistant Staphylococcus aureus infections in the obese patients. Infection and Drug Resistance 2019; 12:877-891. PMID: 31114267.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2019 -	Associate Professor, Rutgers University, The State University of New Jersey, Piscataway, NJ
2019 -	Director, Center of Excellence for Pharmaceutical Translational Research and Education (CEPTRE), Rutgers, The State University of New Jersey, Piscataway, NJ
2022-	Member, FDA Pharmaceutical Science and Clinical Pharmacology (PSCP) advisory committee
2012 - 2019	Assistant Professor, Rutgers University, The State University of New Jersey, Piscataway, NJ
2010 - 2012	Research Assistant Professor, University at Buffalo, SUNY, Buffalo, NY
2008 - 2010	Post-doctoral fellow, University at Buffalo, SUNY, Buffalo, NY

Honors

2021	Honorary Associate Professor in Pharmacy, University of Nottingham, UK
2015	Translational Medicine and Therapeutics Award, Pharmaceutical Research and Manufacturers of America Foundation
2007	Award of Excellence in PhD studies, Faculty of Medicine, The Hebrew University of Jerusalem
2005	Faculty Prize for outstanding MSc Thesis, Faculty of Medicine, The Hebrew University of Jerusalem
2005	Travel grant, Alex Grass Center for Drug Design and Synthesis of Novel Therapeutics

C. Contribution to Science

1. Attaining therapeutic drug concentrations in tissues is required for effective treatment. Direct measure of tissue concentrations in humans is rarely available. Preclinical investigations are often conducted in different species, which complicates the comprehensive analysis of the data. We have developed physiologically-based pharmacokinetic (PBPK) modeling approach for describing the biodisposition of amphotericin B in

preclinical species for nonliposomal (Fungizone) and liposomal drug (AmBisome). The model successfully captured the data from mouse and rat studies. Furthermore, we have developed approaches for incorporating allometric relationships into the PBPK model and accurately predicted concentration of amphotericin B in human tissues. Later, this approach was further developed and applied to anticancer drugs (paclitaxel, doxorubicin, and cisplatin). In addition, Studies and mechanistic model were performed to capture disposition of drugs in various parts of the CNS.

a. Chiang M, Back HM, Lee JB, Oh S, Guo T, Girgis S, Park C, Haroutounian S, **Kagan** L. Pharmacokinetic Modeling of the Impact of P-glycoprotein on Ondansetron Disposition in the Central Nervous System. Pharm Res. 2020 Sep 28;37(10):205. PubMed Central PMCID: PMC8752326.
b. Lee JB, Zhou S, Chiang M, Zang X, Kim TH, **Kagan L**. Interspecies prediction of pharmacokinetics and tissue distribution of doxorubicin by physiologically-based pharmacokinetic modeling. Biopharm Drug Dispos. 2020 Apr;41(4-5):192-205. PubMed PMID: 32342986.
c. Zang X, **Kagan L**. Physiologically-based modeling and interspecies prediction of paclitaxel pharmacokinetics. J Pharmacokinet Pharmacodyn. 2018 Aug;45(4):577-592. PubMed PMID: 29671170.
d. **Kagan L**, Gershkovich P, Wasan KM, Mager DE. Dual physiologically based pharmacokinetic model of liposomal and nonliposomal amphotericin B disposition. Pharm Res. 2014 Jan;31(1):35-45. PubMed PMID: 23793994.

2. The mechanism of subcutaneous absorption of protein therapeutics, including monoclonal antibodies, is not well characterized. Incomplete bioavailability after subcutaneous delivery is a serious obstacle for delivering these drugs. We investigated the role of FcRn (Fc receptor of neonates) in absorption of monoclonal antibodies and described other mechanisms affecting subcutaneous absorption of protein therapeutics. We identified that the dose level, anatomical site of injection, and injection volume may all play an important role in the rate and extent of absorption. Advanced mechanism-based models were developed to describe the role of the lymphatic system, binding to FcRn, and other processes in absorption of proteins. Furthermore, we suggested an approach for increasing the bioavailability of monoclonal antibodies. I performed animal studies and developed the pharmacokinetic models.

a. Gao X, Voronin G, Generaux C, Rose A, Kozhich A, Dalglish G, Rosa R, Oh S, **Kagan L**. Lymphatic Distribution of Etanercept Following Intravenous and Subcutaneous Delivery to Rats. Pharm Res. 2020 Jul 27;37(8):155. PubMed PMID: 32720159.
b. **Kagan L**. Pharmacokinetic modeling of the subcutaneous absorption of therapeutic proteins. Drug Metab Dispos. 2014 Nov;42(11):1890-905. PubMed PMID: 25122564.
c. **Kagan L**, Mager DE. Mechanisms of subcutaneous absorption of rituximab in rats. Drug Metab Dispos. 2013 Jan;41(1):248-55. PubMed PMID: 23129212.
d. **Kagan L**, Turner MR, Balu-Iyer SV, Mager DE. Subcutaneous absorption of monoclonal antibodies: role of dose, site of injection, and injection volume on rituximab pharmacokinetics in rats. Pharm Res. 2012 Feb;29(2):490-9. PubMed PMID: 21887597.

3. Accurate prediction of pharmacokinetic and pharmacodynamic properties from preclinical studies is a difficult task, especially for protein biotherapeutics that exhibit complex nonlinear behavior. We have developed approaches for interspecies modeling and human predictions of pharmacokinetics and pharmacodynamics of other protein therapeutics (cytokines, monoclonal antibodies, etc.) by selective scaling of certain model parameters among species and sharing of other parameters.

a. **Kagan L**, Abraham AK, Harrold JM, Mager DE. Interspecies scaling of receptor-mediated pharmacokinetics and pharmacodynamics of type I interferons. Pharm Res. 2010 May;27(5):920-32. PubMed Central PMCID: PMC3176922.
b. Chen T, Mager DE, **Kagan L**. Interspecies modeling and prediction of human exenatide pharmacokinetics. Pharm Res. 2013 Mar;30(3):751-60. PubMed Central PMCID: PMC3732180.
c. **Kagan L**, Zhao J, Mager DE. Interspecies pharmacokinetic modeling of subcutaneous absorption of rituximab in mice and rats. Pharm Res. 2014 Dec;31(12):3265-73. PubMed Central PMCID: PMC4469501.

4. Good understanding of the underlying dynamics of the disease is required for establishing the efficacy of therapeutic intervention. We developed population disease progression model of knee osteoarthritis using 6 years of follow-up data for more than 1000 subjects in Osteoarthritis Initiative (OAI) database. A series of significant covariates that affect the rate of the disease progression were identified. Furthermore, the model indicated that two different subpopulation exists with different progression patters. This finding may have an important effect on selection of therapeutic intervention for osteoarthritis patients. I was the Principal Investigator on the project and secured funds to perform the research.

    a. Passey C, Kimko H, Nandy P, **Kagan L**. Osteoarthritis disease progression model using six year follow-up data from the osteoarthritis initiative. J Clin Pharmacol. 2015 Mar;55(3):269-78. PubMed PMID: 25212288.

5. Absorption of drugs into the systemic circulation is a complex process that is governed by the interplay between the drug molecule and the gastrointestinal tract. We have developed a surgical animal model that allows for precise control over the rate and the site of delivery of drugs inside the GI tract. This experimental methodology was successfully applied for determining the preferential “absorption window” and effects of GI motility on pharmacokinetics for a series of model compounds with different primary absorption mechanisms. Semi-physiological pharmacokinetic models were developed and incorporated the rates of drug transit through the gut and different absorption characteristics of each of the GI regions.

    a. **Kagan L**, Lapidot N, Afargan M, Kirmayer D, Moor E, Mardor Y, Friedman M, Hoffman A. Gastroretentive Accordion Pill: Enhancement of riboflavin bioavailability in humans. J Control Release. 2006 Jul 20;113(3):208-15. PubMed PMID: 16806558.
    b. **Kagan L**, Hoffman A. Systems for region selective drug delivery in the gastrointestinal tract: biopharmaceutical considerations. Expert Opin Drug Deliv. 2008 Jun;5(6):681-92. PubMed PMID: 18532923.
    c. **Kagan L**, Hoffman A. Biopharmaceutical aspects of gastro-retentive dosage forms: The gabapentin paradigm. Journal of Drug Delivery Science and Technology. 2009; 19(40):233-239.
    d. **Kagan L**, Lavy E, Hoffman A. Effect of mode of administration on guaifenesin pharmacokinetics and expectorant action in the rat model. Pulm Pharmacol Ther. 2009 Jun;22(3):260-5. PubMed PMID: 19166957.

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