BIOGRAPHICAL SKETCH

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NAME: Mackenzie L Cottrell

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

POSITION TITLE: Assistant 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)*	Completion Date MM/YYYY	FIELD OF STUDY
Oklahoma State University, Stillwater, OK	BS	05/2007	Nutritional Sciences
University of Oklahoma Health Sciences Center, Oklahoma City, OK	MS	06/2011	Pharmaceutical Science
University of Oklahoma Health Sciences Center, Oklahoma City, OK	PharmD	06/2011	Pharmacy
ASHP Accredited Pharmacy Residency	Residency	06/2012	Pharmacotherapy
ACCP Accredited HIV Pharmacology Academic Fellowship	Fellowship	07/2014	HIV Pharmacology
ABCP Accredited UNC – Duke Collaborative T32 Postdoctoral Fellowship	Fellowship	07/2015	Clinical Pharmacology

A. Personal Statement

I am Associate Professor within the Division of Pharmacotherapy and Experimental Therapeutics in the UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill. I am a clinical pharmacologist with advanced training in antiretroviral (ARV) pharmacology through the completion of an American Board of Clinical Pharmacology accredited T32 clinical pharmacology fellowship and an American College of Clinical Pharmacy accredited HIV pharmacology fellowship. I have been actively researching in the fields of ARV and HIV cure pharmacology for >10 years and have served as principle, co- or sub-investigator on multiple clinical trials designed to characterize pharmacology within human blood, fluids and tissues using HPLC-MS/MS methodology. Over my research career, I have authored over 100 peer-reviewed abstracts and publications and 3 book chapters describing antiretroviral pharmacology in the context of HIV treatment, prevention, and cure.

From this training and research, I have extensive experience with bioanalytical methods for drug quantification and pharmacokinetic interpretation and modeling. The value of these clinical pharmacology techniques to inform drug development and improve medical therapies has been widely recognized by pharmaceutical industry and regulatory agencies, like the FDA with almost all new drug applications now including components of modeling and simulation. I use my knowledge and experience in clinical pharmacology to assist Center for AIDS Research (CFAR) investigators who require the services of the UNC CFAR Clinical Pharmacology and Analytical Chemistry Core, for which I have served as assistant- or co-director since 2015. Since the creation of the Core in 2004, we have developed methods to quantify >70 chemically distinct molecular entities (including 32 ARV or ARV metabolites and 15 latency reversing agents; LRAs) in >8 biological matrices including plasma, cell culture media, and cell lysates. Because of our boutique approach to bioanalytical chemistry and extensive experience within the HIV research field, we serve a wide array of >80 CFAR investigators each year with their basic and clinical pharmacology research needs. Through this position, I have become well versed in participating in interdisciplinary scientific collaborations.

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

U24 AI179403
NIH (PI: Cottrell, Mackenzie)
01/12/2024-12/30/2028
HIV Pharmacology Data Repository

1R21AI157853
NIH (PI: Cottrell, Mackenzie)
08/01/2021 – 07/31/2024
Accelerating to the Cure: A Novel IVIVE Model for Advancing HIV Eradication Strategies

1R21AI145646
NIH (PI: Cottrell, Mackenzie)
4/09/2019 – 3/31/2022
Feminizing Sex Hormones Impact on PrEP Pharmacology in Transgender Women

1R61AI149499 / 1R33AI149499
NIH/NIAID (MPI: Johnson, Leah (Contact) / Cottrell, Mackenzie)
03/15/2020 – 02/28/2025
Phase I & II: Delivery of Antiretrovirals via Implantable System for Young Children (DAISY)

R01AI176949
NIH (MPI: Benhabbour, Soumya Rahima (Contact), Cottrell, Mackenzie)
07/01/2023 – 06/30/2027
Ultra-long-acting Biodegradable and Tunable Polymeric Solid Implant for HIV Treatment Maintenance

R01MH125671
RTI / NIH (PI: Roberts, Sarah)
03/01/2023 – 07/31/2026
Tu'Washindi: A relationship-focused intervention to reduce GBV and increase PrEP uptake and adherence among Kenyan AGYW

R01AI175068
Boston University / NIH
03/01/2023 – 02/28/2027
Improved Nanoparticle Targeting of Tissue Myeloid Cells for HIV-1 Long-acting Pre-exposure Prophylaxis

B. **Positions, Scientific Appointments, and Honors**

Positions and Employment

2019-	Co-Director, UNC Center for AIDS Research Clinical Pharmacology and Analytical
2015-	Assistant Professor, Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, NC
2015-2019	Assistant Director, UNC Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core, University of North Carolina at Chapel Hill, NC
2012-2015	HIV Clinical Pharmacist, UNC Health Care Infectious Diseases Clinic, Chapel Hill, NC
2011-2012	Per Diem Staff Pharmacist, OU Medical Center – Edmond, Edmond, OK
2009-2011	Pharmacy Intern, OU Medical Center – Edmond, Edmond, OK
2008-2009	Pharmacy Intern, Homeland Pharmacy, Oklahoma City, OK

Other Experience and Professional Memberships

2014-	American Academy of HIV Medicine – Credentialed HIV Pharmacist
2011-2018	American College of Clinical Pharmacy – Board Certified Pharmacotherapy Specialist

Honors

2017	Infectious Diseases Pharmacotherapy Paper Award 2016, Society of Infectious Disease Pharmacists
2012	Outstanding Master's Thesis, Graduate College, University of Oklahoma Health Sciences Center
2011	Merck Award, College of Pharmacy, University of Oklahoma Health Sciences Center

2010 H. Richard Shough Award, College of Pharmacy, University of Oklahoma Health Sciences Center
2010 Graduate Student Association Award, College of Pharmacy, University of Oklahoma Health Sciences Center
2007-2009 Mosier Scholar Award, College of Pharmacy, University of Oklahoma Health Sciences Center
2004-2005 Niblack Research Scholar Award, Oklahoma State University

C. Contributions to Science

1. **Development of long-acting HIV prevention and treatment strategies.** The effectiveness of oral ARV for HIV prevention and treatment hinges on daily dosing strategies. Incomplete adherence to daily dosing can result in breakthrough viral replication, drug resistance, and treatment failure. Developing long-acting alternatives is a high priority opportunity to improve effectiveness. I provide clinical pharmacology support for multiple research programs aiming to develop long-acting antiretroviral formulations by overseeing animal study design and PK analyses. Additionally, I provide dose translation support through an array of modeling techniques including deconvolution and compartmental approaches. Through employing these clinical pharmacology tools, we ensure that only formulations with absorption rates optimized to achieve safe and effective ARV exposure in our target clinical populations are down selected for further development.

    a. Li L, Lee C, Cruz DF, Krovi SA, Hudgens MG, **Cottrell ML**, Johnson LM. Reservoir-Style Polymeric Drug Delivery Systems: Empirical and Predictive Models for Implant Design. *Pharmaceuticals (Basel).* 2022 Oct 3;15(10):1226.
    b. Li L, Gatto GJ, Brand RM, Krovi SA, **Cottrell ML**, Norton C, van der Straten A, Johnson LM. Long-acting biodegradable implant for sustained delivery of antiretrovirals (ARVs) and hormones. *J Control Release*. 2021 Oct 20;340:188-199.
    c. Benhabbour SR, Kovarova M, Jones C, Copeland DJ, Shrivastava R, Swanson MD, Sykes C, Ho PT, **Cottrell ML**, Sridharan A, Fix SM, Thayer O, Long JM, Hazuda DJ, Dayton PA, Mumper RJ, Kashuba ADM, Victor Garcia J. Ultra-long-acting tunable biodegradable and removable controlled release implants for drug delivery. *Nat Commun.* 2019 Sep 20;10(1):4324.
    d. Joiner JB, King JL, Shrivastava R, Howard SA, **Cottrell ML**, Kashuba ADM, Dayton PA, Benhabbour SR. Effects of Injection Volume and Route of Administration on Dolutegravir In Situ Forming Implant Pharmacokinetics. *Pharmaceutics*. 2022 Mar 11;14(3):615.

2. **Secondary data analyses to develop a novel algorithm for HIV pre-exposure prophylaxis (PrEP) adherence monitoring**. Tenofovir diphosphate (TFVdp; an active metabolite of oral PrEP) is measured in DBS to estimate adherence. However, TFVdp's extremely long half-life in whole blood (14 days) may lead to misclassification following recent changes in dosing patterns. PrEP's other metabolite, emtricitabine triphosphate (FTCtp), has a shorter half-life in whole blood that could inform adherence classification; however, concentration thresholds were undefined. We harnessed DBS PK data collected as part of a directly observed therapy (DOT) PK study, ENLIGHTEN (NCT03218592), that aimed to establish a hair imaging technique for adherence monitoring and employed a population PK modeling approach to simulate TFVdp and FTCtp in DBS across different scenarios of PrEP adherence. Through these simulations we characterized misclassification risk, defined FTCtp DBS concentration thresholds, and demonstrated an approach to monitor adherence for event driven PrEP dosing.

    a. Devanathan A, Dumond J, Anderson D, Moody K, Poliseno A, Schauer A, Sykes C, Gay C, Rosen E, Kashuba ADM, **Cottrell ML**. A Novel Algorithm to Improve PrEP Adherence Monitoring Using Dried Blood Spots. *Clin Pharmacol Ther*. In press.

3. **Characterization of antiretroviral pharmacology in mucosal compartments**. The female genital and gastrointestinal tracts are the most common sites of HIV exposure. A multitude of evidence indicates that antiretroviral distribution to these mucosal tissues is highly variable between and within each class of agent. For my postdoctoral research, I characterized the tissue distribution of multiple antiretrovirals, which are being used or under investigation for HIV pre-exposure prophylaxis (PrEP). In

a phase I, dose-ranging, pharmacokinetic study (NCT01330199), I characterized the pharmacokinetics of maraviroc, raltegravir, emtricitabine, and tenofovir disoproxil fumarate (TDF) in the peripheral blood, mucosal fluids, and mucosal tissues over 48 hours following a single dose. I was the first to report differential drug distribution within multiple mucosal tissues from women, finding 2-160-fold greater exposure in the lower gastrointestinal tract compared to the female genital tract for all drugs investigated, except emtricitabine which was 80-280-fold lower. I also observed strong relationships between plasma, mucosal fluid, and tissue drug concentrations for these 4 antiretrovirals.

Using multiple linear regression analysis to quantify these relationships, I was the first to describe the validity of mucosal fluids and plasma as possible surrogates for tissue drug concentrations. By using drug concentration data collected as part of separate pharmacokinetic trials, I was also able to describe significant differences in raltegravir genital tract concentrations among women of different menopausal and HIV-sero statuses. Lastly, I designed and led a phase I clinical trial (NCT02357602) to investigate the intracellular pharmacology and tissue distribution of tenofovir alafenamide (TAF), an investigational pro-drug which generates 7-10-fold higher active metabolite concentrations in peripheral blood compared to the pharmacologically similar pro-drug, TDF. The findings of this study provided the first report that active metabolite concentrations in mucosal tissues of women following a single standard treatment dose of TAF vs TDF were 7-fold lower.

a. **Cottrell ML**, Garrett KL, Prince HM, Sykes C, Schauer A, Emerson CW, Peery A, Rooney JF, McCallister S, Gay C, Kashuba AD. Single-dose pharmacokinetics of tenofovir alafenamide and its active metabolite in the mucosal tissues. J Antimicrob Chemother. 2017 Jun 1;72(6):1731-1740. PMCID: PMC5536328
b. **Cottrell ML**, Srinivas N, Kashuba ADM. Pharmacokinetics of Antiretrovirals in Mucosal Tissue. Expert Opinion on Drug Metabolism and Toxicology. 2015 Jun;11(6):893-905. PMCID: PMC4498566
c. **Cottrell ML**, Prince HMA, Allmon A, Mollan KR, Hudgens MG, Sykes C, White N, Malone S, Dellon ES, Madanick RD, Shaheen NJ, Patterson KB, Kashuba ADM. Cervicovaginal and Rectal Fluid as a Surrogate Marker of Antiretroviral Tissue Concentration: Implications for Clinical Trial Design. J Acquir Immune Defic Syndr. 2016 Aug 15;72(5):498-506. PMCID: PMC4942408

4. **Modeling and simulation to predict effective PrEP dosing strategies.** Truvada, a fixed-dose combination tablet of two antiretrovirals, is the only FDA-approved agent for PrEP. The active metabolites of Truvada (tenofovir diphosphate and emtricitabine triphosphate) inhibit viral replication by competing with the natural HIV reverse transcriptase substrates dATP and dCTP for incorporation into the HIV DNA strand. In the presence of high substrate concentrations, higher concentrations of Truvada's active metabolites' are required to inhibit HIV replication. I have worked extensively to characterize the intracellular metabolism of Truvada in multiple biologic matrices and was the first to describe mucosal tissue concentrations of dATP and dCTP. Notably we found that 80-90% lower concentrations in the lower gastrointestinal tract compared to the female genital tract of healthy women. I developed a novel in vitro model to describe the exposure-response relationship between active metabolites, natural substrates, and HIV infection, and I identified an efficacy target of active metabolite concentrations normalized to natural substrates. When paired with simulated concentration data from a population pharmacokinetic model, my in vitro model predicted that ~80% of the population taking 7 doses a week of Truvada will achieve effective concentrations in the female genital tract vs ~90% in the lower gastrointestinal tract with just 1 dose a week.
These data were the first to provide a pharmacologic basis for the marked discrepancies in adherence requirements that have been observed in Truvada PrEP clinical trials between men who have sex with men and heterosexual women.

a. Dumond JB, Francis O, **Cottrell M**, Trezza C, Prince HM, Mollan K, Sykes C, Torrice C, White N, Malone S, Wang R, Van Dam C, Patterson KB, Hudgens MG, Sharpless NE, Forrest A. Tenofovir/emtricitabine metabolites and endogenous nucleotide exposures are associated with p16INK4a expression in subjects on combination therapy. Antivir Ther. 2016;21(5):441-5. PMCID: PMC5266614

b. Schauer AP, Sykes C, **Cottrell ML**, Prince H, Kashuba ADM. Validation of an LC-MS/MS assay to simultaneously monitor the intracellular active metabolites of tenofovir, emtricitabine, and lamivudine in dried blood spots. J Pharm Biomed Anal. 2017 Oct 31;149:40-45. PMCID: PMC5741486
c. **Cottrell ML**, Prince HMA, Sykes C, White N, Malone S, Dellon ES, Madanick RD, Shaheen NJ, Hudgens MG, Wulff J, Patterson KB, Nelson JAE, Kashuba ADM. A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine. J Infect Dis. 2016 Jul 1;214(1):55-64. PMCID: PMC4907409
d. Srinivas N, **Cottrell M**, Maffuid K, Prince HA, Nelson JAE, White N, Sykes C, Dellon ES, Madanick RD, Shaheen NJ, Gonzalez D, Kashuba ADM. Translational Approach to Predicting the Efficacy of Maraviroc-Based Regimens as HIV Preexposure Prophylaxis. Antimicrob Agents Chemother. 2020 Jan 27;64(2). PMCID: 6985753

5. **Characterization of PrEP Pharmacology in Transgender women**. Female sex hormones (FSH) can modulate antiretroviral pharmacology through complex physiologic mechanisms within mucosal tissues. These mucosal tissues can serve as putative viral reservoirs or the point of HIV transmission. Thus, understanding the interaction between FSH and antiretrovirals has important implications for both HIV pre-exposure prophylaxis (PrEP) and cure research. I have reported significant interactions between menopause status and raltegravir distribution into the female genital tract (FGT) where higher FSH exposure appears to correlate with lower penetration; and more recently, determined that endogenous estradiol and progesterone inversely correlate with efavirenze concentrations in the FGT. I was the first to report that PrEP's active metabolite, TFVdp, was significantly (~7 fold) reduced relative to its competing nucleotide (dATP) in the lower GI tract of transgender women using exogenous estradiol for feminization compared to cisgender individuals not taking hormones; and that this ratio (TFVdp:dATP) was inversely correlated with estradiol and progesterone. These findings are currently under peer review for publication in the journal, *Clinical Infectious Diseases*. Taken together, this research suggests that both endogenous and exogenous FSH may diminish PrEP effectiveness or permit ongoing replication in viral reservoirs.

    a. **Cottrell ML**, Patterson KB, Prince HMA, Jones A, White N, Wang R, Kashuba ADM. Effect of HIV Infection and Menopause Status on Raltegravir Pharmacokinetics in the Blood and Genital Tract. Antivir Ther. 2015;20(8):795-803. PMCID: PMC5242325
    b. Nicol MR, Corbino JA, **Cottrell ML**. Pharmacology of Antiretrovirals in the Female Genital Tract for HIV Prevention. J Clin Pharmacol. 2018 Nov;58(11):1381-1395. PMCID: PMC6333200
    c. **Cottrell ML**, Corbett AH, Chinula L, Msika A, Tegha G, Stanczyk F, Kourtis AP, Tang JH. Female genital tract efavirenz exposure negatively correlates with serum estradiol levels in Malawian women. 22nd International AIDS Conference (AIDS 2018). July 23-27, 2018. Amsterdam, Netherlands. Abstract # THPEB062
    d. **Cottrell ML**, Prince HMA, Schauer AP, Sykes C, Maffuid K, Poliseno A, Chun TW, Huiting E, Stanczyk FZ, Peery AF, Dellon ES, Adams JL, Gay C, Kashuba ADM. Decreased tenofovir diphosphate concentrations in a transgender female cohort: Implications for human immunodeficiency virus preexposure prophylaxis. Clin Infect Dis. 2019 Nov 27;69(12):2201-2204. PMID: 30963179

Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1TCG9c66DV85i/bibliography/42412970/public/?sort=date&direction=ascending.