## BIOGRAPHICAL SKETCH

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NAME: Mackenzie L Cottrell

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

POSITION TITLE: Research 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 a clinical pharmacologist with advanced training in antiretroviral 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 field of antiretroviral (and more specifically PrEP) pharmacology for >6 years and have served as principle, sub or co-investigator on 5 clinical trials designed to characterize the pharmacology of 5 different antiretrovirals within human blood, fluids and tissues through quantification of drug concentrations by HPLC-MS/MS technology. Furthermore, I have published over 30 peer-reviewed abstracts, 30 manuscripts and 3 book chapters describing the pharmacology of HIV treatment and prevention. As such, I have extensive experience with analytical methods for drug quantification and pharmacokinetic interpretation and modeling by which to assist CFAR investigators. I am also well versed in participating within interdisciplinary scientific collaborations through my role as Assistant Director for the UNC Center for AIDS Research (CFAR) Clinical Pharmacology and Analytical Chemistry Core, which provides a wide array of clinical pharmacology services to over 100 CFAR investigations each year.

### B. Positions and Honors

**Positions and Employment**

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

**Honors**

2004-2005 Niblack Research Scholar Award, Oklahoma State University
2007-2009 Mosier Scholar 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
2011 Merck Award, College of Pharmacy, University of Oklahoma Health Sciences Center
2012 Outstanding Master's Thesis, Graduate College, University of Oklahoma Health Sciences Center
2017 Infectious Diseases Pharmacotherapy Paper Award 2016, Society of Infectious Disease Pharmacists

**Other Experience and Professional Memberships**

2017- Society of Infectious Diseases Pharmacists
2014- American Academy of HIV Medicine – Credentialed HIV Pharmacist
2011- American College of Clinical Pharmacy – Board Certified Pharmacotherapy Specialist

## C. Contribution to Science

1. 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. My postdoctoral research focused on characterizing the tissue distribution of multiple antiretrovirals, which are currently 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. Additionally, by utilizing drug concentration data collected as part of separate pharmacokinetic trials, I was able to describe significant differences in raltegravir genital tract concentrations among women of different menopausal and HIV-sero statuses. Lastly, I designed 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.

    1. **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. PMID: 28369415
    2. **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. PMID: 25797064.
    3. **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. PMID: 26999532

2. 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 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, finding 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 doses 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.

1. 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. PMID: 26731175.
2. 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.
3. **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 HIV Pre-Exposure Prophylaxis Outcomes in Men and Women Using Tenofovir Disoproxil Fumarate ± Emtricitabine. J Infect Dis. 2016 Jul 1;214(1):55-64. PMID: 26917574.

3. 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.

1. **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. PMID: 26040011
2. 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. PMID: 29901863
3. **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
4. **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 HIV pre-exposure prophylaxis (PrEP). Clin Infect Dis. 2019 Apr 9. [Epub ahead of print] PMID: 30963179.

**Complete PubMed Bibliography of Mackenzie Cottrell's Published Work:**

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

**D. Research Support**

**Current Research Support**

Award 1R21AI145646 4/09/2019 – 3/31/2021 2.4 cal.
NIH/NIAID; Role: PI
***Feminizing Sex Hormones Impact on PrEP Pharmacology in Transgender Women***
A PK/PD approach will work to fill critical knowledge gaps by 1) assessing drug interactions between feminizing hormone therapy and PrEP and 2) modeling PrEP effectiveness in transgender women

SubAward 5R01AI119346-04 (Apetrei) 8/1/2015-1/31/2020 1.80 cal.
University of Pittsburgh/NIH/NIAID; Role: Subaward PI
***Animal Model for Testing SIV Latency Reversal Strategies***
Development and validation of Romedepsin and prostratin analytical methods in plasma and tissues for pharmacokinetic analysis, modeling and simulation and the design of therapeutic dosing strategies.

SubAward 1R01CA233441 (Heredia) 1/8/2019 – 12/31/2019 1.92 cal.
Universtiy of Maryland Baltimore/NIH/NCI; Role: Subaward PI
***Impact of Concomitant Chemotherapy on HIV Resistance to cART and Reservoir Size***
This proposal will identify combinations of cART and chemotherapy with superior safety and anti-HIV activity that could improve chemotherapy outcomes and decrease cancer deaths in HIV-infected cancer patients.

**Research Support Completed During the Last Three Years**

Grant Number (Margolis) 1/01/2017 – 12/31/2018 1.20 cal.
Qura Therapeutics, LLC; Role: Project Lead
***Qura Project 1F Using a Novel Hollow Fiber Model System to Predict the In Vivo Pharmacodynamics of Latency Reversing Agents***
Development of an *in vitro* dynamic drug exposure model for latency reversing agents to predict *in vivo* pharmacodynamics and optimal dosing.

550KR161708 1/01/2018 – 12/31/2018
NC TraCS Institute and UNC CFAR Developmental Core
*Does Sex Hormone Therapy Decrease TFV/FTC Active Metabolite Formation in Mucosal Tissues?*
Role: Principle Investigator
Clinical trial to describe the impact of feminizing sex hormone therapy on the pharmacology of antiretrovirals in the lower gastrointestinal tract of transgender women.

S120282-3/R01HD072705 6/1/2015 - 5/31/2016
NIH/Eastern Virginia Medical School (PI: Doncel)
Role: Co-Investigator
*Differential HIV infection and Tenofovir activity in pre- and post-menopausal women*
Characterization of tenofovir and tenofovir diphosphate concentrations in the blood and tissues of dosed women and in surgery-derived tissue explants.

5P01MH094177-01-05 SUBACC:Proj 3 6/01/2015 - 5/31/2017
NIH/NIMH (PI: Swanstrom)
*HIV Tropism, Persistence, Inflammation and Neurocognition in Therapy Initiation*
Role: Co-Investigator
Address the issue of persistent viral replication in the CNS while on successful therapy, by defining the role of therapy choice and drug levels in the CNS, and the potential for genetic polymorphism in efflux drug transporters to impact drug concentrations to such an extent as to allow residual, ongoing viral replication.

SubAward MAPS1-16-068/AID-OAA-A-14-00011 (MAPS1), Award Year 3 9/1/2016-8/31/2017
Eastern Virginia Medical School/Agency for International Development
*Pharmacokinetics Testing for: CONRAD A15-140, titled Phase I Exploratory Pharmacodynamic Study of Tenofovir-Based Products*
Role: SubAward PI
Characterization of pharmacokinetics for oral TDF vs tenofovir gel in the blood, female genital and lower gastrointestinal tracts of HIV uninfected women.