Summer 2020 Student Research Program
Project Description

FACULTY SPONSOR'S NAME AND DEGREE: ***Stanley H. Weiss, MD***
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PROJECT TITLE (200 Characters max):

Long Term Cohort Studies of Drug Users and Related Groups

HYPOTHESES:

1) *Our long-term cohorts are uniquely suited to examining the long term outcomes (such as cancer and end stage liver disease) and the dynamics of the HIV and HCV epidemics among adult drug users, using subject-level data.*
2) *These baseline data, such as medical and behavioral factors and biomarkers, as well as new biomarker data, are predictive of specific health and vital status outcomes.*
3) *About 1500 persons (~15%) were studied on two or more occasions, enabling assessment of changes over time in the factors ascertained, etc.*

PROJECT DESCRIPTION **(Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)**

*Clients enrolled in drug treatment programs (including medication-assisted treatment programs) suffer from a variety of disadvantages and medical issues, including access to care, complications from infectious agents, and drug-related problems such as overdoses. We have developed an expanding interdisciplinary team of faculty co-investigators and senior drug treatment program staff to embark on a set of endeavors. Our past cohort studies included systematic administered interviews of treatment program clients using an extensive structured interview we developed asking about their demographics, behaviors; patterns of drug abuse, including opioids, cannabis, other classes of drugs, alcohol and tobacco; and sexual behavior. In study subsets, issues such as overdose and treatment of hepatitis C virus (**HCV**) and for HIV have been explored in detail. We have documented high rates of infection with hepatitis C. Beyond the epidemiology, the health policy and system implications are being explored.*

Current novel findings from our past studies include the association of specific drugs such as tobacco and cannabis with lung cancer, a picture of long-term mortality due to liver failure, the epidemiology and impact of infection with HCV and HIV, occurrence of overdoses, and health issues among male and female drug users with a focus on chronic diseases such as cancer, including hepatocellular carcinoma and lung cancer. From 2016-2019 we enrolled over 300 additional drug users to examine in detail some highly relevant current issues, methadone dosage over a prolonged period of time, and their use of opioids during and out of treatment. This study is helping to provide the basis for our new initiatives.

This project complements and builds upon the several national prospective cohort studies that Dr. Weiss designed in the mid 1980's while he was at the National Cancer Institute (NCI), which totaled about 11,084 enrollments from over about 10,000 persons nationally, including ~2,500 from NJ. He joined the NJMS faculty in 1987. These studies have substantial accumulated medical, laboratory and questionnaire data, plus a linked biospecimen repository of about 100,000 vials. The follow-up period is ~30+ years, with an extensive baseline database. These constitute the only large cohort study of adults

with high rates of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection within New Jersey, and furthermore included both men and women and a diverse racial/ethnic mix, from the start. In September 2012, in the largest material transfer from NIH in legacy UMDNJ history, 82,962 vials were transferred from NCI to Dr. Weiss, supplementing other specimens already held here. Linkage and personal identifying data are known to us. Collaborations have been renewed with many of the original treatment programs and with the NJ Department of Health and the NJ State Cancer Registry, with administrative approvals obtained to repeat various types of registry matching studies to ascertain long-term outcomes.

*NIDA has already completed analysis of >5000 blood biospecimens from our cohort subjects, ascertaining the presence or absence of ~800,000 single nucleotide polymorphisms (**SNP**s, that is, genetic variants) that may affect risk for a broad array of diseases and conditions, including various chronic diseases and cancers, drug addiction, tobacco use, etc. We anticipate analyses both using GWAS approaches (as part of the NIDA Genetics Consortium, of which Dr. Weiss is an active member) as well as creating polygenic models when examining disease outcomes. About 3,000 additional subjects are anticipated to be run on the same genetics array.*

Another ongoing new initiative is the study of metabolomics, including ~4000 compounds such as cannabinoid and nicotine metabolites. Specimens collected in the 1990's are expected to complete laboratory testing in Spring 2020, with data then available for additional analyses in summer 2020.

Assessment of the accrued data is leading to the development with several Rutgers investigators of plans to utilize the biologic repository, contingent upon approval by the IRB of protocols in development or revision. NIDA's genotyping of a large numbers of specimens is planned as the first step in a sequence of laboratory-based analyses of these biospecimens. For example, because most members of these cohorts have a history of injection drug use, the rates of HIV, HTLV-II, and hepatitis C virus (HCV) infection among them are all quite high. Thus, these data have the potential to be a rich resource for finding predictors of mortality due to these infectious agents – such as hepatocellular carcinoma, HCV-associated liver failure and HIV-associated issues. Data sharing agreements with NIDA have been approved by Rutgers.

*Utilizing our linkage information and follow-up data, beginning in 2015 we matched 2,254 persons enrolled from NJ to the NJ State Cancer Registry (**NJSCR**), with over 185 cancers previously documented. Future matching is anticipated to once again include national databases (such as the National Death Index and the Social Security Administration database). In the near term, matching will occur to NJ state-wide databases (such as the New Jersey HIV/AIDS registry) and updating the NJSCR match. Later on, we may again match to the NJ Vital Statistics database and/or the federal National Death Index Plus (**NDI-Plus**). Relevant analyses are ongoing.*

Technology has been evolving over the decades, with laboratory analyses becoming possible on minute amounts of stored material. These tests need to be validated on our stored samples, prior to embarking on large-scale studies. Multiple laboratory-based investigators have expressed interest, and opportunities to do laboratory-based work and related analyses will be evolving.

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have a history of injection drug use, the rates of HIV, HTLV-II, and hepatitis C virus (HCV) infection among them are all quite high. Thus, these data have the potential to be a rich resource for finding predictors of mortality due to these infectious agents – such as hepatocellular carcinoma, HCV-associated liver failure and HIV-associated issues.

Indeed, Dr. Weiss was responsible for detecting and demonstrating an epidemic of HTLV-II in drug users. He also demonstrated immunologic abnormalities associated with HTLV-II, and played an integral role in the FDA's decision to screen blood donors for HTLV-II. The long-term medical effects of HTLV-II, if any, remain to be determined. These cohorts will provide new epidemiologic information about HTLV-II as well as many other infectious agents.

Data were assembled over the last 30+ years from these cohorts using questionnaires and other data collection forms designed by Dr. Weiss and his collaborators. In the approximately three decades since these studies were initiated, advances and standardization of data elements and their design have occurred to facilitate inter-institutional laboratory studies. Such standards include PhenX (www.phenxtoolkit.org) and DataSHaPER (www.datashaper.org), as well as a consortium of large prospective cohort studies that has some support from the National Cancer Institute. We shall assess the compatibility of our data collection with one or more of these standardized formats used in various other large-scale projects, and shall explore the feasibility of transforming our existing data into the most appropriate format. These steps may permit us to join other groups in large-scale data projects. We shall also provide NIH appropriate data, with due attention to confidentiality issues, per national standards. Because of our plans to match our data to the existing national databases described earlier, we will need to be mindful of those data sources' requirements as well as of our existing data if we undertake such transformation.

The detailed specific project based upon our many initiatives and very long-term prospective cohort studies, with an appropriate timeline for a summer project, will be developed with the student based upon her/his past experience, training, and interests. Dr. Daniel M. Rosenblum, Assistant Professor, will also provide mentorship on the project, as will many collaborators from the NJSCR and the Cancer Institute of NJ and other Rutgers faculty.

SPONSOR'S PUBLICATIONS MOST RELEVANT TO THIS RESEARCH:

Recent Abstracts:

- ***SH Weiss**, DM Rosenblum, A Brooks, C Bixby, C Hevi, EO Johnson. Successful Illumina Array Genotyping on Serum Stored For Three Decades. 2020 NIDA Genetics Consortium Meeting at NIDA headquarters, 6001 Executive Blvd, Rockville, MD, January 13-14, 2020.*
- *MN Fahmy, DM Rosenblum, **SH Weiss**. Drug Use Patterns by Education and Employment Status among New Jersey Methadone Maintenance Clients. American Public Health Association 2019 Annual Meeting and Exposition (Alcohol, Tobacco and Other Drugs Section program), Philadelphia, PA (Session 3327.1, Opioid Use Disorders: A Roundtable of Compelling, Conversations).*
- *DM Rosenblum, N Pyrsopoulos, R Wolferz, B Biondi, A Kurland, J Connor, **SH Weiss**. Is curative therapy for infection with hepatitis C virus (HCV) reaching infected drug users? American Public Health Association 2017 Annual Meeting and Exposition (Epidemiology program), Atlanta, GA, Nov 8, 2017 (oral).*

- *R Wolferz, A Kurland, DM Rosenblum, A Mittal, M Pulaski, E Bahrami, J Lomuti, M Fahmy, E Zerbo, M Jaker, **SH Weiss**. Are current drug treatment programs successful in preventing drug overdoses? American Public Health Association 2017 Annual Meeting and Exposition (Epidemiology program), Atlanta, GA, Nov 8, 2017 (oral).*
- *R Wolferz, DM Rosenblum, N Pyrsopoulos, A Kurland, M Pulaski, **SH Weiss**. A minority of drug users infected with the hepatitis C virus have received curative treatment. American Public Health Association 2017 Annual Meeting and Exposition (Medical Care section), Atlanta, GA, Nov 6, 2017.*
- *NT Pyrsopoulos, DM Rosenblum, J Connor, R Wolferz, A Kurland, M Pulaski, P Patel, **SH Weiss**. HCV-infected persons in the USA: Identification, current treatment needs, and obstacles to care. American Association for the Study of Liver Diseases (AASLD), The Liver Meeting®, Washington, DC, Oct 20-24, 2017.*
- *Savan Kabaria, Jessica Connor, Breanne E. Biondi, Matt Pulaski, Daniel M. Rosenblum, Stanley H. Weiss. Human T-Cell Lymphotropic Virus Type II Infection Is Associated with Increased Medical Mortality in a National Long-term Cohort of Injection Drug Users. 14th Annual AMA Research Symposium – Medical Student Section. Walt Disney World Swan and Dolphin Resort, Orlando, Fla. Nov 11, 2016. (Mr. Kabaria is NJMS Class 2019.)*
- *SH Weiss, BE Biondi, Antoinette Stroup, Sumathy Vasanthan, Karen Pawlish, Daniel M. Rosenblum. Hepatocellular carcinoma in a 30-year prospective cohort study of 2200 HCV-infected adults**.** Abstract #362311. 144th American Public Health Association Annual Meeting & Expo, Denver, Oct. 29 - Nov. 2, 2016.*
- *Breanne E. Biondi, Sumathy Vasanthan, Anita Thomas, Karen Pawlish, Daniel M. Rosenblum, Arjun Gupta, Antoinette Stroup, Stanley H. Weiss. Methodological issues in matching cohorts to registry data: results from a large, long-term, prospective study. 4th Epidemiology Congress of the Americas, Miami, FL, June 21-24, 2016.*

Past Relevant Student Summer Projects:

- *O'Shaughnessy MG (NJMS 2022). Cohort Studies of Drug Users and Related Groups. 2019*
- *Ahuja S (NJMS 2022). Cohort Studies of Drug Users and Related Groups. 2019*
- *Karajgikar RM (TCNJ/NJMS 2022/2025). Cohort Studies of Drug Users and Related Groups. 2019*
- *Agrawal PV (NJIT/NJMS 2022/2025). Cohort Studies of Drug Users and Related Groups 2019.*
- *Tang NC (TCNJ/NJMS 2022/2025). Cohort Studies of Drug Users and Related Groups. 2019*
- *Chen K (TCNJ/NJMS 2022/2025). Cohort Studies of Drug Users and Related Groups. 2019*
- *Patel R (TCNJ 2021). Cohort Studies of Drug Users and Related Groups. 2019*
- *Patel SM (NJMS 2021). Studies of Drug Users and Related Groups. 2018*
- *Chilakapati R (TCNJ/NJMS 2021/2024). Studies of Drug Users and Related Groups. 2018*
- *Randhawa A (TCNJ/NJMS 2021/2024). Studies of Drug Users and Related Groups. 2018*
- *Muenzen RM (NJMS 2020). Studies of Drug Users and Related Groups. 2017*
- *George LC (NJMS 2020). Studies of Drug Users and Related Groups. 2017*
- *Peddireddy S (TCNJ/NJMS 2020/2023). Studies of Drug Users and Related Groups. 2017*
- *Patel J (TCNJ/NJMS 2020/2023). Studies of Drug Users and Related Groups. 2017*
- *Kabaria S (NJMS 2019). Follow-up of Long-Term Prospective Cohort Studies of Injection Drug Users and Related Groups. 2016*
- *Connor JA (NJMS 2019). Follow-up of Long-Term Prospective Cohort Studies of Injection Drug Users and Related Groups. 2016*
- *Pulaski MR (NJMS 2019). Current issues among New Jersey drug users. 2016*
- *Kaushal N (NJMS 2019). Cancer Outcomes in The Long-Term Prospective Weiss Cohort Studies: New Jersey Cohorts. 2015.*
- *Eltoukhy H (NJMS 2015). Characterization of Two Prospective Cohorts for their Use in a Bio-Specimen Repository at NJMS. In: 2011 Summer Student Research Abstracts, New Jersey Medical School, pp. 13-17.*

- *Knox KR (NJMS 2003). Comparison of Cancer Incidence in HIV+ and HIV- Injection Drug Users: 15-Year Follow Up of a Cohort Study. New Jersey Medical School Summer Student Research Abstracts 2001; Abstract # 35.*

Journal Publications (selected):

- *Weiss SH, Ahuja Sonali (NJMS Class of 2022): F1000Prime Recommendation of [Shover CL et al., Proc Natl Acad Sci USA 2019 116(26):12624-12626]. In F1000Prime, 07 Aug 2019;* DOI 10.3410/f.735955392.793563337 . *Commentary on: Association between medical cannabis laws and opioid overdose mortality has reversed over time.*
- *Weiss SH, Skurnick J, Zhao C, Henrard D. Mortality due to hepatic failure among a cohort of injection drug users: a preliminary report from the United States. Workshop on viral hepatitis and HIV infections. Anales de Medicina Interna Octubre:57-58, 1995.*
- *Hisada M, Chatterjee N, Kalaylioglu Z, Battjes RJ, Goedert JJ. Hepatitis C virus load and survival among injection drug users in the United States. Hepatology 42:1446-1452, 2005.*
- *Hisada M, Chatterjee N, Zhang M, Battjes RJ, Goedert JJ. Increased Hepatitis C Virus load among injection drug users infected with Human Immunodeficiency Virus and Human T Lymphotropic Virus Type II. The Journal of Infectious Diseases 188:891–7, 2003.*
- *Goedert JJ, Fung MW, Felton S, Battjes RJ, Engels EA. Cause-specific mortality associated with HIV and HTLV-II infections among injecting drug users in the USA. AIDS 15:1295-1302, 2001.*
- *Briggs NC, Battjes RJ, Cantor KP, Blattner WA, Yelin FM, Wilson S, Ritz AL, Weiss SH, Goedert JJ. Seroprevalence of human T cell lymphotropic virus type II infection, with or without human immunodeficiency virus type 1 coinfection, among US intravenous drug users. The Journal of Infectious Diseases 172:51-58, 1995.*
- *Cantor KP, Weiss SH, Goedert JJ, Battjes RJ. HTLV-I/II seroprevalence and HIV/HTLV coinfection among U.S. intravenous drug users. Journal of the Acquired Immune Deficiency Syndromes 4:460-467, 1991.*
- *Wiktor SZ, Jacobson S, Weiss SH, Shaw GM, Reuben JS, Shorty VJ, McFarlin DE, Blattner WA. Spontaneous lymphocyte proliferation in HTLV-II infection. Lancet 337:327-328, 1991.*
- *Wang RY-H, Grandinetti T, Shih JW-K, Weiss SH, Haley CL-D, Hayes MM, Lo S-C. Mycoplasma genitalium infection and host antibody immune response in patients infected by HIV, patients attending sexually transmitted diseases (STD) clinics and in healthy blood donors. FEMS Immunology and Medical Microbiology 19:237-245, 1997.*
- *Caussy D, Weiss SH, Blattner WA, French J, Cantor KP, Ginzburg H, Altman R, Goedert JJ. Exposure factors for HIV-1 infection among heterosexual drug abusers in New Jersey treatment programs. AIDS Research and Human Retroviruses 6:1459-1467, 1990.*
- *Beretta A, Weiss SH, Rappocciolo G, Mayur R, Cosma A, De Santis C, Quirinale J, Robboni P, Shearer GM, Berzofsky JA, Villa ML, Siccardi AG, Clerici M. Seronegative intravenous drug users at risk for HIV exposure exhibit antibodies to HLA class I antigens and T-cells specific for HIV envelope. The Journal of Infectious Diseases 173(2):472-476, 1996. (Cited in April 29, 1996 issues of Blood Weekly and of Vaccine Weekly.)*
- *Heredia A, Joshi B, Weiss SH, Lee SF, Muller J, Poffenberger KL, Quirinale J, Epstein JS, Hewlett IK. Absence of evidence of retrovirus infection in intravenous drug users with idiopathic CD4+ lymphocytopenia. The Journal of Infectious Diseases 170:748-749, 1994.*
- *Weiss SH, Klein CW, Mayur RK, Besra J, Denny TN. Idiopathic CD4+ T-lymphocytopenia. Lancet 340:608-609, 1992.*
- *Weiss SH, Goedert JJ, Sarngadharan MG, The AIDS Seroepidemiology Collaborative Working Group, Gallo RC, Blattner WA. Screening test for HTLV-III (AIDS agent) antibodies: specificity, sensitivity and applications. The Journal of the American Medical Association 253:221-225, 1985.*

- *Weiss SH, Cowan EP. Laboratory detection of human retroviruses. In: AIDS and Other Manifestations of HIV Infection, 4th edition, ed. Gary P. Wormser, Elsevier Science, London. Chapter 8, pp. 147-183, 2004.*
- *Robert-Guroff M, Weiss SH, Giron J, Jennings AM, Ginzburg HM, Margolis I, Blattner WA, Gallo RC. Prevalence of antibodies to HTLV-I, -II, and -III in intravenous drug abusers from an AIDS endemic region. The Journal of the American Medical Association 255:3133-3137, 1986.*

IS THIS PROJECT SUPPORTED BY EXTRAMURAL FUNDS?

Yes or No ☒

(IF YES, PLEASE SUPPLY THE GRANTING AGENCY'S NAME)

For some of the activities performed outside of NJMS, existing grants and contracts from the National Institute on Drug Abuse (NIDA) are employed:

- ***NIDA grant # 1R01DA044014-01 to Eric O. Johnson, PhD, PI, at RTI International;***
- ***NIDA contract to RUCDR Infinite Biologics.***

THIS PROJECT IS: ☒Clinical ☒Laboratory ☒ Behavioral ☐ Other

THIS PROJECT IS CANCER-RELATED☒

Please explain Cancer relevance:

- *A major emphasis is currently on the detailed examination of our lung cancer and liver cancer outcome data.*
- *The ongoing follow-up in conjunction with the NJ State Cancer Registry and matches to the NJ AIDS/HIV registry will enable us to assess risk factors for cancer and progression in these well-defined cohorts, and understand aspects of the AIDS epidemic over three decades of time.*
- *Hepatitis C virus (HCV) infection (which a study drawn from these cohorts was the very first to demonstrate is highly prevalent in injection drug users) is a major cause of hepatocellular carcinoma with a latency on the order of decades. Better understanding of biomarkers in HCV-infected individuals that are correlated with occurrence of hepatocellular carcinoma can lead to more effective use of medical resources to prevent this cancer. Another key outcome is end stage liver failure.*
- *HIV and HTLV-I infection are linked with specific types of cancers.*
- *Beyond immunologic abnormalities, a health impact of HTLV-II remains to be determined. This project is uniquely suited to examine this issue due to the high prevalence of HTLV-II, plus the study's size and longevity.*

THIS PROJECT IS HEART, LUNG & BLOOD- RELATED☒

Please explain Heart, Lung, Blood relevance:

A major emphasis is currently on the detailed examination of our lung cancer outcome data.
Specimens that have been collected and that could be examined for biomarkers include sera, plasma, urine, Ficoll-hypaque purified lymphocytes, and EBV-transformed cell lines, and viral isolates.
Data from these studies were instrumental in the decision by the US FDA that all blood products be screened for HTLV-II. The demonstration that these retroviruses were highly prevalent in these specimens helped lead to setting the early policies in the state of NJ concerning testing for HIV, and on the FDA's approach to test licensing. The results from this study will be relevant to U.S. screening practices of potential blood donors.

THIS PROJECT EMPLOYS RADIOISOTOPES☐

THIS PROJECT INVOLVES THE USE OF ANIMALS ☐

PENDING ☐ APPROVED ☐ IACUC PROTOCOL #

THIS PROJECT INVOLVES THE USE OF HUMAN SUBJECTS ☒

PENDING ☒ APPROVED ☒ IRB PROTOCOLS #'s Pro20150001314, Pro20160000704 (both approved), & Pro2019002287 (pending).

Summer 2020 Student Research Program
Project Description

THIS PROJECT IS SUITABLE FOR:

UNDERGRADUATE STUDENTS	☐	ENTERING FRESHMAN	☐
SOPHMORES	☐	ALL STUDENTS	☒

THIS PROJECT IS WORK-STUDY: **Yes** ☒ **or** **No** ☐

THIS PROJECT WILL BE POSTED DURING ACADEMIC YEAR FOR INTERESTED VOLUNTEERS?: **Yes** ☒ **or** **No** ☐

WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?

- *Receive training in confidential study procedures.*
- *How to design follow-up analyses in cohort studies, such as nested-case control designs.*
- *Strategies for efficient use of health data.*
- *How to approach the analysis of datasets.*
- *How to perform critical and systematic assessment of methodologies, and their practical applications.*
- *How critical assessment of findings can lead to changes in approach or implementation.*
- *How to understand and utilize power calculations in setting project objectives and goals that appear feasible.*
- *For those who include a laboratory based component, how to conduct lab analyses and assess results.*
- *For those who assist in our field work: receive training in conducting in-person interviews using a written questionnaire, and develop comfort working with staff and subjects in novel outpatient settings.*

CRITICAL PRIOR EXPERIENCE AND SKILLS

- *Prior experience in performing data analysis and in using data analysis software such as SAS, SPSS or R is REQUIRED; there is insufficient time during the summer period to newly learn and become expert in SAS programming and to perform new data analyses on the considerable new data we are continually receiving.*
- *Prior experience with software such as MS Excel and the Microsoft Office Suite.*
- *Excellent written and communication skill is REQUIRED.*
- *Human subjects protection training and certification through the Rutgers-specified CITI course for Social, Behavioral, and Epidemiologic Research Investigators. (See orra.rutgers.edu/citi for details.) Certification will be REQUIRED at least 6 weeks prior to starting, to give adequate time to be added to our current IRB protocol.*

USEFUL ADDITIONAL RELEVANT PRIOR EXPERIENCE AND SKILLS

(Note: Only some of these skills are requisite for a specific project. However, some skill(s) are important to enable getting a jump-start.)

- *In conjunction with another, new study - prior fieldwork experience in urban areas, including client interviewing and/or administration.*
- *Prior experience working on a research team.*
- *If interested in a lab-associated component: prior relevant lab experience.*
- *Car and driver's license (for projects involving access to community sites).*