

Introduction

A substantial amount of basic biomedical research can be done in tissue culture, mice, or other models like fruit flies. However, some questions about human disease really can only be addressed in primates. There may be anatomical reasons, as in the case of reproductive systems, or in areas like behavior and the brain, which require more sophisticated cognition to be relevant to humans.

The ONPRC research portfolio encompasses multiple disease-related areas. Almost all areas of human disease and disorders are studied, with an emphasis on genetics, reproduction, development and aging, behavioral and systems neuroscience, and heart, metabolic and infectious diseases. Researchers here also study infectious disease with the OHSU Vaccine and Gene Therapy Institute. One of the few things not modeled in monkeys at this time is cancer.

AGING/LONGEVITY

- **Teaming up to ensure healthy aging:** To respond to the world's ballooning aging population, researchers at ONPRC teamed up with physicians, human-based researchers, support organizations, and seniors themselves to assure that the necessary resources and knowledge is in place. **(OHSU Healthy Aging Alliance)**
- **Prevent or reverse age-related dementia:** ONPRC investigators were the first to discover a mechanism that prevents new neurons from forming in old brains. This discovery provides a new path for investigating ways to prevent or even reverse age-related dementia — promoting the formation of neurons and preventing their decline. **(Sherman Lab)**
- **Hormone therapy for postmenopausal brain health:** ONPRC investigators determined whether ovarian hormone therapy in middle-aged, menopausal monkeys would help cognition. Across a one-year testing period, treatment with the estrogen hormone estradiol improved and maintained spatial working memory and visuospatial attention. **(Kohama, Neuringer Labs)**

AIDS

Preventing, treating and stopping HIV/AIDS and other global diseases

- **Using human monoclonal antibodies to protect babies born to mothers with HIV** by treating within a single dose given the first few days after birth. This passive antibody cocktail is safe and non-toxic and prevents permanent establishment of the virus in the body, so that no additional treatment is necessary. **(Haigwood, Hessel Labs)**
- **Developing an HIV/AIDS vaccine candidate that may have the ability to completely clear HIV from the body** – Research into cytomegalovirus (a disease carried by a majority of the population) has revealed unique characteristics of the disease - discovered in part by ONPRC scientists – that may help in the battle to prevent AIDS. This work resulted in additional funding from the prestigious Bill & Melinda Gates Foundation. **(Picker, Nelson, Sacha, and Frueh Labs)**
- **Research towards an HIV Cure** – ONPRC scientists are gaining new insights into strategies that lead to HIV remission and eventually a cure, by better understanding where in the body and how the virus persists and testing promising approaches to eliminate the virus, ranging from novel

therapeutic drugs that target latently infected cells to hematopoietic stem cell transplantation approaches. **(Estes, Okoye, Picker, and Sacha Labs)**

CELL AND GENE THERAPIES

Gene therapy

- **Using advances in gene editing to understand human disease** –ONPRC scientists are using newly developed gene-editing techniques to understand susceptibility to viral infections and the development of human diseases such as blindness and deafness. The findings from these studies will provide the necessary insight to develop new therapies for their cure. **(Hennebold Lab)**
- **Curing blindness:** ONPRC and the Casey Eye Institute have begun human clinical trials to treat macular degeneration, a major cause of blindness. The work is based on ONPRC research documenting a genetic basis to the disorder and piloting gene therapy prior to the human studies. **(Neuringer Lab)**

INFECTIOUS DISEASES

Vaccine Development

- **Demonstrating a new and improved approach to virus inactivation in the production of vaccines.** Researchers at ONPRC have shown that using hydrogen peroxide as a virus inactivator causes less damage to the virus and results in more potent vaccines. A vaccine against West Nile virus was tested in macaques before moving forward to Phase I clinical trials and other vaccines against yellow fever, zika, dengue, chikungunya, and Campylobacter (which causes >400 million cases of diarrhea each year) are also showing early success in animal models with Phase I clinical trials scheduled to begin in 2021 for yellow fever and chikungunya **(Slifka Lab)**
- **Infectious disease vaccine development** – Researchers developed a promising new cytomegalovirus-based vaccine approach that has greatly improved the outlook on making a vaccine for HIV/AIDS, as well as for other global diseases, including TB, West Nile virus, and malaria. **(Picker, Frueh, Slifka, Wilder Labs)**
- **Improving our understanding of immune memory** that may result in needing fewer vaccinations. Researchers at ONPRC found the mechanism for long-lived immunity after tetanus vaccination by following tetanus-specific antibody responses for 10 years in rhesus macaques **(Slifka Lab)**
- **Hepatitis B virus.** There are currently 247 million people worldwide with chronic hepatitis B virus infection, which often leads to liver dysfunction and cancer. The recent discovery of a cure for hepatitis C virus has rejuvenated efforts to cure hepatitis B virus infection. ONPRC is teaming up with pharmaceutical companies and academic institutions to test new therapies designed to cure chronic hepatitis B virus infection. **(Burwitz Lab)**

OBESITY

- **Metabolic effects of polycystic ovary syndrome (PCOS)** – ONPRC scientists have developed an NHP model of PCOS to evaluate the separate and combined effects of elevated androgen levels and diet-induced obesity that are difficult to address in clinical studies due to the obesity present in most

women diagnosed with PCOS. These studies have shown that a western-style diet exacerbates the effects of the basic hyperandrogenemia that defines PCOS. **(Roberts, Varlamov labs)**

- **New experimental model of type-1 diabetes** - using Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technology, ONPRC investigators have developed a novel mouse model of type-1 diabetes in which insulin production can be reversibly inhibited to produce an insulin-deficient diabetes state in which to test therapies such as designer insulins and other approaches. The basic technology is translatable to the NHP, which will result in a true preclinical model of type-1 diabetes. **(Kievit, Roberts labs)**
- **Effects of obesity and insulin resistance on response to SIV infection and antiretroviral therapy (ART)** – ART increases the risk of obesity and diabetes in people with HIV. ONPRC researchers are using the NHP model to determine whether pre-existing obesity/prediabetes increases the risk for and the severity of ART-associated metabolic comorbidity. **(Roberts, Kievit labs)**
- **Understanding the relationship of the brain and body weight issues** - Improved understanding of the role of the brain in the development of lifelong body weight issues. Findings regarding the role of the brain in controlling weight gain, research to may help combat the obesity epidemic.

REPRODUCTIVE HEALTH

Fertility & Pregnancy

- **Preserving cancer survivors' ability to have children** – Many current cancer therapies in use today are also toxic to a woman's eggs. Research at ONPRC is focusing on finding ways to protect the eggs residing in the ovary during chemo and radiation therapies. The center is developing methods to remove and freeze portions of the ovary so that they can be transplanted back into individuals after the end of their cancer treatment and thereby restore fertility. **(Xu, Zelinski Labs)**
- **Making birth control better, safer, and more accessible** – Research at ONPRC has highlighted new birth control methods that may be safer, more effective and more convenient than current methods. Center scientists are also developing novel, nonsurgical permanent contraceptive methods that would be available to women in settings with limited healthcare resources **(Hennebold, Jensen, Slayden, and Zelinski Labs)**
- **Increasing infertility treatment success rates** - Scientists at ONPRC have identified factors in the ovary that may predict the ability of an egg to fertilize and develop into an embryo that leads to a pregnancy. **(Chavez, Hennebold Labs)**
- **Vaginal microbiome** – Research at ONPRC has examined the microbiome of female rhesus macaques and is developing a model to study bacterial vaginosis. **(Slayden and Slifka Labs)**
- **Identifying genetic abnormalities in embryos before implantation** – Researchers at ONPRC have devised an automated imaging system for embryos that are cultured after in vitro fertilization to help predict which ones possess genetic anomalies and, therefore, would not likely result in a term pregnancy. **(Chavez Lab)**
- **Understanding causes of infertility** – Studies underway at ONPRC are providing insights into how abnormal levels of the hormone testosterone in the circulation and a high fat diet interact to impact female fertility. **(Chavez, Hennebold, Slayden Labs)**

Fetal and Newborn Health

- **Defining how the placenta impacts fetal growth and development** – The placenta serves as a critical interface between the mother and fetus. ONPRC scientists are using state-of-the-art imaging systems to evaluate the impact of marijuana use or maternal nutrition on placental function and how it translates to pregnancy outcomes and the health of the offspring. **(Frias Lab)**
- **The relationship between infection during pregnancy, preterm birth, and infant health** – Intrauterine infection during pregnancy can lead to preterm birth. Studies being conducted at ONPRC define how babies born prematurely due to infection during pregnancy alters normal developmental processes. **(Kelleher Lab)**
- **Preventing birth defects in babies born to moms infected with Zika virus** – Zika infection during pregnancy leads to a greatly increased risk of abnormal development of the baby's brain. Studies underway at ONPRC are revealing how viral infection during pregnancy compromises fetal growth and development. The results of these studies will guide the creation of vaccines that protect against infection and are safe for both mother and baby. **(Frias, Kelleher, Streblow Labs)**
- **Infant formula and eye health** - Information learned at the ONPRC about the role various ingredients in breast milk play in healthy eye development has resulted in changes in infant formula world-wide. **(Neuringer Lab)**
- **Paternal contributions to offspring health** – Children conceived by older fathers are at elevated risk for a number of human diseases. The basis of this paternal age effect is poorly understood, but appears to be linked to DNA mutations that accrue in sperm. ONPRC researchers are studying the genomes of exceptionally large primate families, some with over 100 children from one father, to better understand the causes and consequences of these age-related mutations **(Conrad Lab)**.

SUBSTANCE USE AND ABUSE

Alcoholism and Addiction

- **Battling deadly addiction** – Alcoholism is the third leading cause of preventable death in the US. Research at ONPRC is revealing risks for becoming addicted to alcohol, such as changes in gene sequence, alterations in gene expression, young adult stage of life, menstrual cycle phase, and aggressive temperament that suggest possible methods of preventing or treating alcoholism. **(Grant Lab)**
- **Finding markers in blood that reflect the alcohol addicted brain:** For the first time, modifications to genes important in alcohol addiction were shown to be similarly modified in blood and brain cells. The data provide a new way to characterize the alcohol-addicted brain of individuals with a blood test. **(Grant, Ferguson Labs)**
- **Combatting the effects of nicotine when pregnant women continue smoking** - ONPRC research has revealed that vitamin C has the ability to prevent some of the damages to fetal lungs caused by women smoking while pregnant. The research has led to a new treatment with the goal to shield unborn babies from the damaging impacts of nicotine when pregnant women are unable to stop smoking. **(Spindel, McEvoy Labs)**
- **Understanding the effects of marijuana use in pregnancy** – Marijuana is the number one illicit drug used in pregnancy, but there is limited literature to guide obstetric providers and patients regarding

contemporary use. Research at ONPRC combines novel imaging, histology, and neurobehavioral assessment to understand the impact of chronic prenatal marijuana exposure on placental and offspring development. **(Lo, Kroenke, Sullivan Labs)**

- **Developing a non invasive marker of adverse fetal alcohol exposure:** Exposure to alcohol in utero is the greatest cause of abnormal brain development in the western hemisphere. Many women consume alcohol prior to knowing they are pregnant and this research is aimed at developing MRI imaging biomarkers of adverse alcohol exposure in the first trimester. This knowledge can help with early identification for infants that would benefit from early intervention approaches to mitigating behavioral and cognitive deficits associated with fetal alcohol exposure **(Cuzon Carlson, Kroenke, Sullivan labs)**

OTHER CATEGORIES

Brain Disorders

- **Combating multiple sclerosis** - Scientists at ONPRC have discovered a naturally occurring disease in monkeys that is very much like multiple sclerosis in humans — a discovery that could have a major impact on efforts to understand the cause of and treat multiple sclerosis. **(Sherman, Wong, Rooney Labs)**
- **Gene therapy for Huntington’s Disease** - This debilitating and fatal disease is caused by a mutation in a known gene. Scientists at the ONPRC have pioneered selectively targeting deep brain structures to replace the defective gene. In doing so, they have also opened up a new surgical and MRI technologies for manipulating brain circuitry involved in other brain disorders. **(McBride, DCM, Kroenke Labs)**
- **Adolescent health** - During the next 10 years, more than 3.7 million children will be diagnosed with pubertal timing disorders in the United States. Early or delayed timing of puberty is associated with increased risks for oncogenic, cardiometabolic, gynecological, gastrointestinal, musculoskeletal, and neurocognitive disorders. We now know that environmental factors like nutritional status, exposure to light, chronic disease and endocrine disruptors are capable of influencing neuroendocrine development. Using non human primate and rodent models, researchers at ONPRC are studying the gene networks and epigenomic modifications associated with the environmental impact on pubertal timing. **(Lomniczi Lab)**

Cardiovascular Disease

- **Investigating the origins of atherosclerosis**– Research at ONPRC is uncovering how the interaction between platelets and the blood vessel wall contributes to the early development of atherosclerotic plaque. **(Lindner Lab)**
- **Improving tissue and organ blood flow** – Researchers at ONPRC are leveraging their important discovery of how ultrasound increases blood flow in tissues to create new therapies for atherosclerotic disease. **(Lindner, Hinds Labs)**
- **Developing new artificial blood vessels** – The creation of artificial blood vessels that are better accepted by the human body will lead to much longer lifespan of these grafts in patients, and are being tested at the ONPRC. **(Hinds Lab)**

In vivo Imaging

- **Visualizing how the brain processes information** - The brain is compartmentalized into areas that are specific for receiving sensory information (smell, sight, etc.), placing that information in context and acting on that information. Many brain disorders are due to relatively subtle miscommunications in this process. Researchers at the ONPRC are pushing the envelope of brain “connectivity” with MRI imaging sensitive to diet, drugs, and personality measures (**Kroenke, Costa, Neuringer, Sullivan, Grant, Cuzon Carlson, McBride Labs**)
- **Maternal and Fetal Health** - Scientists at the ONPRC have developed approaches that focus on fetal health by imaging the function of the placenta and the growth of organs with high resolution. The technological breakthrough will allow rapid transfer of early diagnostics to mitigate developmental disorders. (**Kroenke, Frias, Grant, Kievit, Labs**)
- **Molecular Imaging Technologies** – Scientists from all Divisions have engaged in research programs developing and using novel "smart" imaging probes that are able to detect the molecular or cellular processes responsible for disease development and for evaluating the response to new therapies. These novel probes have been used in diseases including atherosclerosis, viral infections such as HIV, neurologic disease, placental insufficiency, and heart attack.

Other

- **Blood volume calculation techniques**- Total circulating blood volume is an important critical care parameter and current means of estimating blood volume are often inaccurate or even misleading. Using nonhuman primates, we have developed a novel technique for objectively measuring blood volume quickly, accurately, safely, and inexpensively using a durable, hand-held device. We expect wide-ranging application of this technique for military and civilian trauma care. (**Dr. Ted Hobbs**)
- **Effects of sedatives and/or anesthetics on the developing brain**- Sedation and/or anesthesia early in life can lead to varying degrees of brain cell damage in humans and other animals. Further, early anesthetic exposure may be linked to the development of learning disabilities and ADHD in children. Nonhuman primates are not only helping us to understand the acute effects of sedatives and anesthetics on the developing brain, but are also aiding in the development of protective agents that can reduce the impact of such exposure in infants and children. NHPs have also allowed us to study the long term cognitive and behavioral effects of exposure to certain anesthetics early in life. (**Dissen, Coleman/Martin- DCM**)
- **Protecting infants from diarrheal disease** - Each year, 760,000 children under 5 years of age die of diarrheal disease. Survivors experience changes in intestinal architecture and microbiome that contribute to growth stunting and delayed cognitive development. Researchers at ONPRC are evaluating the histologic and microbiome changes that naturally occur in infant rhesus with diarrheal disease. We have developed a vaccine that protects adults and juvenile macaques from *Campylobacter*-associated diarrheal disease. We are currently evaluating whether the vaccine will reduce *Campylobacter*-associated diarrhea and improve microbiome diversity and growth in rhesus infants. (**Drs. Kamm Prongay, Andrew Haertel, and Mark Slifka**)
- **Genetic models of human disease** – Through careful collaboration among pathologists and geneticists, 9 rare genetic diseases have been identified to be naturally occurring in the ONPC breeding colony. All of these correspond to a human disease, some of which cannot currently be studied due to a lack of model. Genetic model identification will open new opportunities in the development of treatments and cures for debilitating disease (**Ferguson, Conrad, Bimber, Lewis labs**).