

## *Selected milestones in PMS/MACS research 1982-2008*

1982- DR RINALDO STUDIES NEW “GAY DISEASE” AT UNIVERSITY OF PITTSBURGH. Because of his interest in herpesviruses, Dr. Charles Rinaldo and Pitt medical student David Lyter approached local lesbian and gay leaders, and bar owners to initiate a pilot study in response to the new disease seen primarily among gay and bisexual men, first called GRID (Gay-Related Immune Deficiency), then AIDS.

1983 - MULTICENTER AIDS COHORT STUDY (MACS) FUNDED. The National Institutes of Health (NIH) funded five centers (Pittsburgh, Chicago, Los Angeles, Baltimore, and San Francisco) to study the natural history of AIDS. The Pittsburgh initiative is named the “Pitt Men’s Study”. All but San Francisco collaborate to form the MACS and establish a national specimen repository.

1984 - PITT MEN’S STUDY BEGINS RECRUITMENT. Pitt Men’s Study researchers began recruiting Tri-state Area men by visiting bars, having picnics in North Park, and going to other places where gay and bisexual men gather. Over 1,200 are eventually recruited for the Pittsburgh portion of the MACS.

1985 - HIV ANTIBODY TESTING INITIATED: MACS clinic sites began testing for HIV antibody as indication of infection. PMS volunteers are invited to learn the results of these tests.

1986 - STANDARDS OF HIV PROGNOSIS ESTABLISHED. MACS scientists begin to develop standard prognostic markers of immune suppression during HIV infection.

1987 - ROLE OF SEXUAL BEHAVIOR LINKED TO TRANSMISSION OF HIV. MACS publishes benchmark data concerning sexual behaviors and their role in the transmission of HIV.

1989 - DIFFERENT SURVIVAL TIMES DOCUMENTED FOR HIV INFECTED MEN. MACS researchers documented longer survival times for many HIV-infected men, yet note that 10% progress to clinical AIDS within four years of infection. Intensive investigation of long-term survivors and rapid progressors is undertaken to determine intervention strategies.

1990 - HEPATITIS B VIRUS TRANSMISSION EFFICIENCY DOCUMENTED. Pittsburgh MACS investigators showed that HBV is transmitted almost 9 times more efficiently than HIV in gay men.

1990 - INCREASED RISK OF PNEUMOCYSTIS CARINII PNEUMONIA (PCP) NOTED AMONG MEN INFECTED WITH HIV-1: MACS data showed that PCP is unlikely to develop in HIV-1-infected patients unless their CD4T cells are depleted to 200 per cubic millimeter or below or the patients are symptomatic, and therefore set the standard of care that prophylaxis should be reserved for such patients.

1990 - AUTOPSY PROGRAM BEGINS: Autopsies are not easy for volunteers, and their families and loved ones to contemplate. Yet they are vital for the complete understanding of HIV disease and the role of the clinically undiagnosed illness in AIDS. The MACS established an autopsy protocol, which all four adopt for use.

1991 - NATIONAL T CELL STANDARDS ESTABLISHED FOR HIV. The MACS established quality control standard for flow cytometry (T cell counts) that is also adopted by the national, multisite, NIH AIDS Clinical Trials Group.

1991-1993 - IMPACT OF ZIDOVUDINE (ZDV) TREATMENT AND PCP PROPHYLAXIS DOCUMENTED. MACS researchers documented that ZDV treatment and PCP prophylaxis extended AIDS-free time by 6-9 months and that the most common complications included CMV retinitis, esophageal candidiasis, and wasting syndrome.

1992 - ZDV MONOTHERAPY AND PCP PROPHYLAXIS SHOWN TO SLOW PROGRESSION TO AIDS. MACS data support the hypothesis that in HIV-1 infection, early treatment with ZDV and PCP prophylaxis improves survival in addition to slowing the progression to AIDS.

1993 - MACS NEUROPSYCHIATRIC STUDY PROVIDED FOUNDATION FOR THE EVALUATION OF THE MECHANISMS RESPONSIBLE FOR HIV-ASSOCIATED NERVOUS SYSTEM DISEASE. MACS research indicated that the development of AIDS is linked to increase risk of HIV-associated dementia (HAD), although cognitive impairment can occur before the onset of AIDS. The research also indicated that HAD can develop with a cumulative prevalence as high as 20%, and an annual incidence of 7-10% following a diagnosis of AIDS.

1993 - IMPACT OF DEPRESSION AND OUTCOME OF HIV INFECTION SHOWN. MACS research showed that mental depression does not relate to worse outcomes of HIV infection.

1994 - THE PRODUCTION OF INTERFERON ALPHA BY BLOOD DENDRITIC CELLS IN RESPONSE TO HIV AND OTHER VIRUS INFECTIONS IS DEMONSTRATED. Pittsburgh MACS investigators were the first to show that a subset of dendritic cells produced very high levels of the antiviral protein, interferon alpha. These cells may thereby act to regulate HIV infection and other immune responses

1995 - FACTORS INFLUENCING PROGRESSION VS. NON-PROGRESSION ARE DELINIATED. 10-15% of infected men have stable T-cell counts over a 10-year period; intensive investigation were conducted to understand why. The amount of virus in the blood, genetic factors, the character of the initial course of HIV disease and the exposure to sexually transmitted disease after being infected with HIV were found to be related to progression to AIDS.

1995 - NONPROGRESSION OF HIV INFECTION RELATED TO LOWER VIRAL TISSUE BURDEN AND HIGH ANTI-HIV CYTOTOXIC T LYMPHOCYTES (CTL): Dr. Fauci's NIH laboratory in collaboration with the MACS showed that lymph nodes harbor low levels of virus in long term non-progressors. The Pittsburgh MACS reported that this is related to high levels of anti-HIV-CTL.

1995 - DISCOVERY THAT FAILURE OF T-CELL HEMOSTASIS PROCEEDS AIDS. MACS investigators showed that over 75% of HIV infected men have a dramatic, sharp drop in total T cell number in blood about 1.5 years before the onset of overt AIDS. This implied that a critical change in the virus and/or the host is common in most HIV-infected persons and may serve as a target for treatment intervention.

1996 - VIRAL LOAD IDENTIFIED AS PREDICTOR OF HIV PROGRESSION: Pittsburgh MACS investigators identified a strong relationship between HIV viral load and clinical progression to AIDS. Based on this research, viral load became the standard measure for prognosis of HIV infection and initiation of antiviral drug therapy.

1996 - DISCOVERY OF NEW VIRUS THAT CAUSED KAPOSI'S SARCOMA (KS): Utilizing specimens that include those from the MACS autopsy repositories, Drs. Moore and Chang at Columbia University identified a new herpesvirus, termed KSHV, that is the cause of KS, the major type of AIDS cancer.

1996 - GENETIC BASIS FOR INCREASE OR DECREASE IN PROGRESSION RATE OF HIV INFECTION IDENTIFIED. NIH scientists in collaboration with the MACS show that host genetic factors were linked to both slower and faster progression of HIV infection. These studies had important implications for the development of treatment and vaccines for HIV.

1997 - SEMEN IDENTIFIED AS THE MAJOR VEHICLE FOR VIRAL TRANSMISSION THROUGHOUT THE COURSE OF HIV INFECTION: Researchers in the Pittsburgh MACS identified high levels of HIV in semen at all stages of the infection. The study indicated that viral load decreases in semen following therapy with potent antiretroviral drugs, decreasing the likelihood of HIV transmission.

1997 - FUNCTIONAL CAPACITY OF DENDRITIC CELLS IN HIV INFECTION DELINEATED: Research conducted by Pittsburgh MACS investigators indicates that dendritic cells had the capacity to stimulate antigen-specific CD8 T cell immunity even late in infection. This set the foundation for development of dendritic cell-based immunotherapy of HIV infection.

1998 - TRIPLE DRUG THERAPIES TESTED AS TREATMENT FOR AIDS: The effectiveness of triple drug therapies in the restoration of CD4 and CD8 T cells, and the significance of decreases in HIV viral load, was confirmed by the MACS on a population basis.

2001 - PREVALENCE OF LIPODYSTROPHY IN MEN WHO ARE HIV INFECTED OR AT RISK OF HIV INFECTION DEMONSTRATED. The prevalence of mild, moderate, and severe body changes ARE documented in HIV-positive men receiving a range of treatments. This pathology had important implications for the use of antiretroviral drugs.

2001 - FIRST DESCRIPTION OF PRIMARY INFECTION WITH KSHV DOCUMENTED. Pittsburgh MACS investigators documented the acute, primary syndrome of KSHV infection in non-HIV infected persons as mildly symptomatic with development of antibodies and T cell immunity.

2003 - IMPACT OF HIV INFECTION AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ON SERUM LIPIDS IN MEN IDENTIFIED: The MACS led by Pittsburgh investigators for the first time documented the impact of HIV infection and HAART on changes in cholesterol levels that could influence development of cardiovascular disease.

2004 – ROLE OF PERSISTENT GB VIRUS C INFECTION AND SURVIVAL IN HIV-INFECTED MEN IDENTIFIED. MACS researchers showed that GBV-C viremia was significantly associated with prolonged survival among HIV-positive men 5 to 6 years after HIV seroconversion. Understanding the mechanisms of interaction between GBV-C and HIV provided insight into the progression of HIV disease.

2005 - IMPACT OF ANTIRETROVIRAL THERAPY ON DEVELOPMENT OF DIABETES MELLITUS AND INSULIN RESISTANCE DEMONSTRATED. MACS investigators highlighted the increased risks associated for development of diabetes and impaired glucose metabolism among HIV-infected men taking HAART.

2006 - A NEW PATTERN OF FAT ACCUMULATION IN HIV-INFECTED MEN DOCUMENTED. Pittsburgh MACS investigators identify a peculiar pattern of body habitus changes in HIV infected men.

2006 - NEW RECEPTOR FOR THE KS VIRUS DISCOVERED. Pittsburgh MACS investigators identify DC-SIGN as a new receptor for infection by KSHV. This is important for developing methods for drug treatment of KSHV infection and prevention of KS.

2007 - PROGNOSTIC VALUE OF HIV RNA, CD4 T CELL COUNT AND SLOPE IN PROGRESSION TO AIDS AND DEATH IN UNTREATED HIV INFECTION ESTABLISHED. The prognostic strength of HIV RNA load in the blood was shown to be consistent with a central role of viral replication in AIDS pathogenesis, supporting the use of HIV1 RNA levels for estimating prognosis in untreated HIV-1 infection.

2007- DISCOVERY THAT DC-SIGN ON B LYMPHOCYTES IS REQUIRED FOR TRANSMISSION OF HIV TO T LYMPHOCYTES: Pittsburgh MACS investigators

discover that DC-SIGN on B cells serves as a portal for HIV-1 infection of T cells, which could be important in the pathogenesis of HIV-1 infection.

2008 – LOWER RISK OF CORONARY ATHEROSCLEROSIS AMONG HIV-INFECTED AND HIV-NEGATIVE MEN: Pittsburgh investigators lead MACS studies that showed a lower risk of coronary atherosclerosis among HIV-infected men than previously understood. This work forms the basis for a new way of thinking about the risk of atherosclerosis in the context of HIV infection.