A poster of Albert Einstein greets visitors to Howard Gendelman's office. It is Einstein's spiritual force that dominates Dr. Gendelman's drive for excellence.

The dementia detective

by Elizabeth Kumru

Howard Gendelman, M.D., answers questions about his research into the mysteries of dementia.

Expand on your theories of the role of inflammation in neurodegenerative diseases.

An inflammatory response is inexplicitly linked to a number of degenerative states including, but not limited to, cancer, arthritis, cardiovascular disease and numerous autoimmune diseases. There is now compelling evidence that HIV dementia, Alzheimer's and Parkinson's diseases (AD and PD) also induce significant brain inflammatory responses, which are initiated by the activation of immune cells through misfolded proteins that occur with age and genetics. This leads to the secretion of a number of neurotoxic products that contribute to nerve cell degeneration. The long-term use of non-steroidal anti-inflammatory drugs (NSAID) decreases the risk for developing AD and PD and delays disease onset. We think anti-inflammatory drugs work by inducing changes in protein metabolism, aggregation and/or by directly diminishing inflammation in the brain. Scientists in our center and department collectively seek to harness inflammation and turn it from bad to good.

What's new in Alzheimer's disease and Parkinson's disease?

Without any doubt AD and PD are the most common neurodegenerative diseases. AD alone affects 4.5 million Americans, and at least $100 billion is spent a year on direct care alone. PD is close behind. Both are progressive neurodegenerative disorders known by impairments in memory, difficulty in balance and walking; tremors, limb stiffness and behavioral deficits. As time ensues and the disease progresses, individuals develop profound dementia with severe memory losses that affect their daily activities and the lives of their loved ones. Genetics can play a role in the development of disease, however advancing age is the most significant disease link. Plaques, fibrils and aggregated proteins are features of pathology, but they alone are not sufficient to generate nerve cell loss. Neurotoxic factors initiated from inflammatory responses by immune activated glial cells appear to be the best link to neurologic deterioration.

Are vaccines feasible for these diseases?

Absolutely! A clear connection exists between inflammation and neurodegeneration and finding ways to slow or prevent it remains our major

AT A GLANCE

Howard E. Gendelman, M.D.

Larson Professor of Internal Medicine and Infectious Diseases

Professor and Chair of Pharmacology and Experimental Neuroscience

Dr. Gendelman joined UNMC in 1993, after having served in faculty positions at Johns Hopkins Medical Institutions, the National Institute of Allergy and Infectious Diseases, the Uniformed Services University of the Health Sciences and the Walter Reed Army Institute of Research. At UNMC, he founded the Center for Neurovirology and Neurodegenerative Disorders (CNND) and developed it into a new interdisciplinary research platform investigating common mechanisms for neurodegenerative diseases that involve inflammation, including AIDS, Alzheimer's and Parkinson's diseases. The center has gained international recognition over the past decade.

research directive.

The unexpected role of T-cells in neuronal outcomes led to research efforts that target immunity in order to enhance neuroprotection. It appears that immunization can increase local production of multiple immune and neurotrophic factors within the injured tissue and generate new directives for studies of neuro-immune interactions and brain regeneration.

However, detailed data is lacking and mechanisms, when uncovered, will likely prove as complicated as many other inflammatory mediators themselves. We must proceed with caution because immunization could also accelerate disease, induce encephalitis or cause autoimmunity.

As a group, we are now developing research strategies that explore specific T-cell types, studied to affect changes in the immune response as well as to best understand the genetics of diseased brain cells and how to repair them. Other ongoing efforts explore improved means to deliver drugs into the brain and new ways to use old drugs for the benefit of the host.

Explain your laboratory's exciting advancement in AIDS treatment.

We've shown that the daily HIV/AIDS multiple pill regimens can be reduced to a single monthly injection using a nanotechnology drug delivery system that we developed with Baxter Healthcare Corporation.

By using macrophages (the cells that carry HIV throughout the body) we can successfully deliver anti-retroviral drugs directly to tissues where the virus grows. We engineered an anti-HIV drug nanoformulation with available HIV-combating drugs and fed large amounts to macrophages. As macrophages migrate to tissues where HIV grows, the drug is secreted. In this way the same cell that spreads virus infection could also stop viral growth and reduce the toxicities commonly seen by conventional pills. Such approaches could be of considerable help in such underdeveloped countries as Africa.

How did you grow the CNND from one person to well over 100?

It's taken a bit of sweat, some vision and incredible support from our administration, local donors and philanthropies and sustained and directed support from the National Institutes of Health. It doesn't hurt to be surrounded by an absolutely outstanding group of scientists and administrators from students, technologists, and postdoctoral fellows to senior faculty. I have been blessed with the right ingredients, time, people and place to do our work at UNMC. I cannot think of a better mix of talent than what we have here in Nebraska. UNMC is indeed the best place to do biomedical research.

As a new chairman, what changes do you foresee for the merged departments of pharmacology and experimental neuroscience?

There are a number of challenges facing our department as well as all those engaged in teaching and biomedical research. The shrinking federal budget and research funds remain significant. Doing more with fewer resources is a challenge for us all. Most of us understand that the days of individual investigator directed research are all but evaporated and being replaced with collaborative interdisciplinary research efforts that span multiple disciplines and research technologies.

The best setup is what we have – a department driving a research center and a center driving departmental administration. But, our strength still revolves around the center structure that generates federal grants, trains graduate and postgraduate students, and provides a foundation for our national and international reputations.

What is your vision/direction for the department and the CNND?

Pharmacology has evolved into cell biology, biochemistry, molecular biology, immunology and drug studies all wrapped into one. Simply put, there is no single discipline. I see team-directed efforts that are strong, interdisciplinary and competitive on the world stage. We will tackle some of the most pressing and difficult questions of human disease and develop new answers to incurable diseases.

The development of young and promising investigators, and the ability to give them the right environment, tools and assistance to realize their dreams is our charge. There are many opportunities to build pharmacology and neurosciences on campus and for our university at large.