Research led by Drs Michael Powell and Vincent Bond is set to have a groundbreaking impact on the global study of HIV and AIDS. Here, the team gives an insight into the significance the work

To begin, could you provide a brief introduction to the pathophysiology of HIV/AIDS?

Individuals who become infected with HIV initially respond in a manner similar to any other viral infection. Many HIV-infected individuals report symptoms similar to those of mononucleosis during the acute phase of infection. However, instead of recovery, infection with HIV leads to a gradual decline of the immune system over a period of years. The decline is manifested as a loss of CD4+ lymphocytes; chronic immune activation and a general dysregulation of the immune system are additional hallmarks of the infection. Eventually, loss of immune function leads to increased susceptibility to a host of opportunistic infections that can be fatal.

Based on more than 10 years of research, how much do you know about the transition from HIV to AIDS and the role of negative regulatory factor (Nef) in this transition?

We are beginning to understand some of the answers to a fundamental question in HIV/AIDS – why infection with HIV leads to AIDS. During HIV infection the Nef protein exerts a variety of effects due to its ability to interact with host cellular proteins. Research from our group suggests that a major cause of pathogenesis induced by infection with HIV is the production of large numbers of vesicles called Nef exosomes. Growing evidence suggests that Nef exosomes are at least partially responsible for the loss of CD4+ T cells and could play a major role in the dysregulation of the immune system.

Who is in your team and what skills do they bring to your research?

Apart from ourselves, we also have, and have had, many dedicated graduate students, postdocs (who are now faculty members) and technicians in our labs over the past 15 years. We are lucky to have a community of researchers both in Atlanta and beyond who have contributed over the years. Participating individuals include Dr Francois Villinger from the Yerkes National Primate Research Center, Dr Wendy Armstrong from the Ponce de Leon Center AIDS clinic, as well as Dr Richard Pollard and Dr James Hildreth – both of whom come from the University of California, Davis, among others.

Could you offer an overview of the Morehouse School of Medicine’s (MSM’s) research programme? Does it confer advantages over other institutions?

MSM is a young medical school that is a part of the Atlanta University Center (AUC), a collection of historically black colleges and universities. The main advantage of MSM lies in a small group of dedicated HIV/AIDS researchers who have worked together for over 15 years on this problem. Our research is aided immensely by the National Institutes of Health (NIH)/National Institute on Minority Health and Health Disparities (NIMHD) Research Centers at Minority Institutions (RCMI) programme, our collaborations as a part of the Emory/MSM Center for AIDS Research (CFAR) and the Atlanta Clinical Translational Institute (ACTSI). These are all excellent resources to which many investigators do not have access.

Recent advances, such as a Mississippi team functionally curing HIV in a baby and French scientists uncovering that early treatment in adults can also functionally cure the disease, have been offering hope to sufferers. How far away are we from curing HIV/AIDS?

Incrementally, we have seen great strides made in the treatment of HIV/AIDS. There is every reason to believe that this will continue. We believe that, at some point, we will be able to look back and see that HIV/AIDS has become a treatable disease. New strategies such as ours could provide another link in a chain that will help turn HIV into a treatable viral infection.

Does HIV/AIDS research receive enough pharmaceutical and government backing? Do you think more needs to be done to highlight that the illness is still a major global problem?

HIV/AIDS is undoubtedly a global problem. We need to develop solutions that are within the reach of anyone infected with HIV. Our challenge is to make sure that we are not satisfied with treatments that mainly impact those in resource-rich countries. We need the will to continue to fight HIV/AIDS globally. The problems associated with treatment of HIV/AIDS have humbled us more than once. It is vital to work more intelligently with the resources we have available.
The power of Nef

Negative regulatory factor is a protein encoded by primate lentiviruses, including HIV. It is a subject of investigations underway at the Morehouse School of Medicine in the US, the results of which are proving vital to both the understanding and treatment of HIV and AIDS.

WORLD HEALTH ORGANIZATION (WHO) statistics have revealed that there are 34 million sufferers of HIV worldwide. Since the clinical discovery of AIDS in 1981, closely followed by the identification of HIV as the underlying pathogen, research in this area has advanced significantly. Indeed, earlier this year the quest to cure HIV was spotlighted when a two year old child who had the virus at birth was seemingly cured.

One factor key to enhancing understanding of and improving treatment methods for HIV is a small protein called negative regulatory factor (Nef). Nef has been shown to play a crucial role in the development of AIDS in HIV-infected individuals. Although it is not required for replication in the laboratory, it is one of a number of pathogen-expressed accessory proteins which function to manipulate the host's cellular makeup and thus promote infection and pathogenesis. An example of Nef’s role in HIV development is the fact that individuals infected with HIV lacking an intact nef gene exhibit reduced or delayed progression to AIDS. The expression of Nef early in the viral life cycle ensures T cell activation and the establishment of a persistent state of infection; two basic attributes of HIV infection.

Drs Michael Powell and Vincent Bond from the Morehouse School of Medicine (MSM) in Atlanta, USA have dedicated the past decade to investigating how infection with HIV ultimately leads to AIDS. Nef is central to these studies and results have demonstrated that the protein could prove vital to unravelling the complexities of these devastating afflictions.

WHY STUDY NEF?

Setting the Nef protein at the centre of their research has enabled Powell and Bond, along with members of their wider research group, to establish key information and make a number of important observations regarding the relationship between Nef and HIV, as well as the relative importance of Nef to simian immunodeficiency virus (SIV). To date, the team’s work has evolved swiftly, with one discovery catalysing the next; all of which contribute to an evolving approach to clinical treatment methods for the virus.

For example, one of the project’s initial findings was that soluble Nef can induce programmed cell death – apoptosis – in a variety of cell types. Instances of such cell destruction were observed in T cells – a group of immune cells that is depleted during infection with HIV. This knowledge led the team to map specific regions within Nef, from both HIV and SIV, which are required for this effect. This indicated that Nef interacts with a receptor on the surface of T cells known as CXCR4. Using these preliminary results, the researchers were able to demonstrate that an interaction between apoptotic regions of Nef and the CXCR4 receptor on cells is at least one of the mechanisms responsible for cell death.

IDENTIFYING EXOSOMES

A more recent development in the study has been the identification of small virus-sized packets called exosomes – vesicles secreted from many types of cells which play key roles in cell-to-cell communication in a number of cell types including immune cells.

There is a growing understanding of the fundamental role of these vesicles in HIV. The team discovered that Nef is secreted from HIV-infected cells in exosomes, which were found to be present in the plasma of infected individuals. Subsequent investigations have revealed that Nef is responsible for modifying cellular trafficking pathways which lead to exosome release. In essence, HIV was proven to be hijacking this cell communication mechanism to promote the virus’ programme; which involves packaging Nef in exosomes, in turn leading to pathogenesis.

This discovery was fundamental to further important observations, such as the fact that Nef exosomes are released from infected cells in greater quantities than virus. The researchers also found that these vesicles are present in the blood of HIV-infected individuals and appear to persist even after levels of virus have been reduced by antiretroviral drugs commonly used to treat HIV infections. This important finding sets the stage for developing new therapies based on limiting the secretion of Nef exosomes.

ADAPTING TECHNIQUES

The profound snowball effect of Powell and Bond’s Nef research has compelled their labs to quickly develop new techniques for the isolation and characterisation of exosomes. Amongst these methods are differential centrifugation, magnetic beads and proteomics. Additionally, with the help of collaborators from the Yerkes Primate Center and University of California, Davis, Powell and Bond have been collaborators on Nef’s role in HIV/AIDS for 15 years.
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EXOSOMES, A WIDER SIGNIFICANCE

In addition to the interesting connection between exosomes and HIV, the research has also led to the realisation that exosomes could play a key role in other disorders. The cellular trafficking pathways, which are now known to lead to exosome release, are involved in a host of cellular processes that are dysregulated and induce various diseases: cancer, arthritis and several infectious diseases involve a similar process. Thus, the strategy to block exosome release could prove invaluable in future treatments for a variety of conditions.

The knowledge of how Nef can facilitate its own release into exosomes also suggests ways in which other proteins could be loaded into exosomes. Such a strategy could be used to produce better vaccines or means of manipulating intracellular signalling to affect a large variety of diseases.

PLANS FOR THE FUTURE

Although they have had much success to date, the scope of Powell and Bond’s future ambitions is equally ambitious. Their research on Nef exosomes has highlighted the role that exosomes play in both maintaining health and causing disease. Thus, the researchers hope to further promote understanding of how exosomes function and how they can be directed to treat other diseases in the future. The scientists believe that a better understanding of basic mechanisms, such as how exosomes function to modulate the immune system, could lead to improved treatments and better outcomes. With their already wide-ranging knowledge on the topic, there is little doubt that the team will continue to expand their knowledge and improve outcomes for HIV patients.