Dr Blossom Damania describes her team’s advancements in the domain of viral oncogenesis, and details international efforts to quash cancer in collaboration with Dr Dirk Dittmer.

**Can you outline the focus and main objectives of your current research?**

My research focuses on the study of oncogenic (cancer causing) viruses. We study Kaposi’s sarcoma-associated herpesvirus (KSHV), which is associated with three different human cancers. Our investigations focus on how this virus manipulates cells to induce oncogenesis, and we perform preclinical studies to establish the efficacy of novel therapies to treat viral cancers. We also study how the virus interacts with the host immune system and establishes lifelong infection in the human host. In sum, our research is focused on the intersection of cancer biology, virology and immunology.

**How has your work evolved over the course of your career, and what are the driving forces that have guided you?**

I have always been keenly interested in understanding the basic mechanisms of how oncogenic viral proteins alter host cell biology. Over the years, we have identified several key cellular signal transduction pathways that are altered by viruses, and have used these insights to target critical pathways and translate our basic science findings into clinical application. Discovery research has always been the driving force behind our work, and realising its translational potential has been compelling and rewarding.

**What unique challenges do oncogenic human herpesviruses such as KSHV pose, and how does your group approach these?**

There are a number of oncogenic viruses that exist in the human population. These include KSHV, human papillomavirus (HPV), Epstein-Barr virus (EBV), hepatitis C virus (HCV) and hepatitis B virus (HBV), to name just a few. Oncogenic herpesviruses are characterised by their ability to persist for life in the host and thereby contribute to cancer development. In latent infection, viral gene expression is limited and the viral genome remains associated with the cell for many generations without virus production. However, during the lytic phase there is a temporal order of viral gene expression resulting in the production of infectious viral progeny.

The mechanism by which KSHV induces cellular transformation is currently unknown, and our lab focuses on understanding how the virus transforms cells and persists in them. We also study basic cellular and viral mechanisms that determine how KSHV is able to maintain the latent and lytic phases of its lifecycle, and the mechanisms by which the virus evades the host immune system. This allows us to develop therapeutics that curb viral replication and prevent virus persistence, thus allowing us to translate basic research into clinical application.

**Your team identified a family of human genes encoding tousled-like kinases (TLK). What are the implications of this finding?**

KSHV and the related oncogenic herpesvirus, EBV, establish lifelong latent infection in the human host. The dormant state of these viruses is what makes it so difficult to treat these infections, and thus the cancers with which they are associated. My lab found that TLK suppressed the activation of the lytic cycle (one of the two stages of the viral lifecycle) of both EBV and KSHV. Hence, by targeting these kinases it may be possible to make these viruses more vulnerable to anti-viral treatments.

**What are some of the goals and current achievements of the Program in Global Oncology (GO) at University of North Carolina (UNC) at Chapel Hill?**

Cancer is a global problem. The World Health Organization and American Cancer Society estimate that by 2030 the majority of cancer deaths will occur in low- and middle-income countries, and so the rising cost of cancer care will be a major burden. The goal of GO is to investigate cancers that disproportionately affect low-income countries, either due to genetic components, population characteristics or oncogenic virus infection.

So far our achievements have been in cancer diagnosis and preclinical studies, which represent the cornerstone for treatment and research. We have implemented essential infrastructures in low- and middle-income countries, and are developing new approaches to diagnose and treat cancers in these countries. UNC GO partners with many institutions and individuals all around the world, such as in India, Malawi, Brazil, South Africa, Zambia, Kenya and China.

**Where will you be focusing your attention in the future?**

Unfortunately, we are still years away from understanding the finer molecular details that define viral cancers. Some proven cancer prevention strategies, such as increased screening for cervical cancer, which offer near-term benefit, have been essential for curbing malignancy. Developing new cancer treatment options, however, is a long-term commitment. It requires a level of trust and partnership between our team in the US and our overseas partners. We hope to build partnerships in cancer research which survive changing administrations and the inevitable setbacks typical of any research effort.
Global problem, global solution

Research at the University of North Carolina at Chapel Hill is levelling the playing field in the fight against virally induced cancer, an endeavour paired with the University’s international project – Global Oncology

THE PHRASE ‘FINDING a cure for cancer’ has assumed the idiomatic definition of achieving the unachievable; but for oncology researchers like Dr Blossom Damania, it is just another day at the office. Damania’s team at the University of North Carolina at Chapel Hill (UNC) is channelling its efforts towards demystifying a particularly tricky form of cancer, that which results from viral infections.

An estimated 20-25 per cent of cancer cases worldwide are caused by infectious diseases; of those, most can be traced back to so-called ‘oncoviruses’. Viral oncogenesis, the process by which these oncoviruses evoke tumour formation in their host, is yet to be delineated in full. Making great strides in this field is the UNC’s Lineberger Comprehensive Cancer Center, of which Damania is an eminent member.

Damania’s research focuses chiefly on Kaposi’s sarcoma-associated herpesvirus (KSHV), which is implicated in Kaposi’s sarcoma and a number of other human cancers. Working at the interface of infection and cancer, Damania’s group is credited with having identified critical pieces of the viral oncogenesis puzzle. By studying the influence of KSHV proteins on host cell signalling pathways associated with cell proliferation, the researchers elucidated the means by which the virus hijacks cellular machinery to promote oncogenesis.

Working in collaboration with fellow virologist, Dr Dirk Dittmer, Damania is co-Director of UNC’s ambitious Program in Global Oncology (GO), highlighted by the National Cancer Institute (NCI)’s Centre for Global Health as among the top five such programmes in the US.

A GLOBAL INITIATIVE
The programme aspires to correct the disproportionately high incidence and fatality rate of cancer in low-income countries across the world. This ambitious mission statement is not without manifestation; GO boasts clinical sites in some seven countries, enacting infrastructural and diagnostic improvements in the regions where cancer hits hardest.

GO also represents a novel approach to the issue of resource scarcity, which defines the low-income countries in which it operates. ‘The ‘colonial-style’ answer to this issue has been to harvest material in low-income countries and analyse it in another, capitalising on the strengths of each region. This still represents one of the more economic solutions, but on its own is no longer an effective option,” Dittmer explains. “Our approach has been to invest in local research infrastructure and talent.”

Working in synergy with the Center for Global Health, a research support network unveiled by NCI in 2011, and the NCI Office of HIV and AIDS Malignancy (OHAM), GO draws on the expertise of a host of UNC researchers and clinicians. While viral oncogenesis is its current focus, plans are in place to extend its remit to include other cancers based on their regional importance.

A GLOBAL PERSPECTIVE
In 2007, GO was founded with a simple adage in mind: what we learn globally will help us locally. The US stands to benefit greatly from GO partnerships, adding to a sizeable list of diseases remedied by US scientists abroad, and thus advancing the nation’s competitive edge in medical research. The partnerships are set to provide newer treatment modalities to cancer patients afflicted with the same disease all over the world, including cancer patients in highly developed countries.

The principal motive for GO, however, is the fact that some forms of cancer are common, and fatal, but can only be studied in regions where their prevalence is particularly high. “For example, Kaposi’s sarcoma, a cancer caused by KSHV, is more common in some parts of Africa than prostate cancer is in the US. As a result of this disparity, the treatment regimen for Kaposi’s sarcoma, even in the US, has not changed since the 1980s,” GO’s co-Directors explain. “Hence studying this cancer in higher regions of prevalence will afford global benefits to patients afflicted with this cancer in both low- and high-income countries.”

Another example, underscoring the importance of an international perspective in cancer research, is breast cancer; common globally, this disease differs in its biology and treatment response between continents. In conducting clinical trials for oncological interventions outside of the US, GO accounts for the immense diversity of the world’s population, thus furthering our understanding of cancer, and ensuring the efficacy of a given intervention is not limited by geographical borders.
UNIVERSITY OF NORTH CAROLINA-CHAPEL HILL (UNC) PROGRAM IN GLOBAL ONCOLOGY

OBJECTIVE
Addressing growing international disparities in cancer incidence and death using UNC faculty expertise in cancer, virology, AIDS-associated malignancies, global cancer prevention and global clinical trials.

KEY COLLABORATORS
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DR BLOSSOM DAMANIA is the Boshamer Distinguished Professor of Microbiology and Immunology at the Lineberger Comprehensive Cancer Center at the UNC-Chapel Hill. She obtained her Doctorate in Cell and Molecular Biology at the University of Pennsylvania in 1998, followed by a postdoctoral fellowship at Harvard Medical School prior to joining the faculty at UNC in 2000. She is currently the Co-Director of the Program in Global Oncology and co-leader of the Virology Program at the Lineberger Cancer Center, and an Assistant Dean of Research in the School of Medicine at UNC-Chapel Hill.

DIRK DITTMER received his PhD at Princeton University and did postdoctoral training at Stanford University and UC San Francisco, USA. He is currently Professor of Microbiology and Immunology at UNC Chapel Hill, the Director of the Lineberger Vironomics Core and Co-Director of the Lineberger Program in Global Oncology.

The programme aspires to correct the disproportionately high incidence and fatality rate of cancer in low-income countries across the world

A GLOBAL SOLUTION
Similar to breast cancer in its worldwide prevalence, cervical cancer is caused by human papillomavirus (HPV). Cervical cancer is therefore often preventable with the use of HPV vaccines; but there is a catch. The genetic constitution of HPVs is subject to variation, and a given vaccine’s efficacy is dependent on the make-up of the specific HPV in question. Dittmer and colleagues are investigating subtypes of HPV that account for invasive cervical cancer cases in Africa in order to utilise HPV vaccines as effective preventive medications.

Damania, Dittmer and their team are also studying the aetiology and tumorigenesis of lymphomas and oral cancers in India.

These studies aim to improve the lives of cancer patients worldwide and justify the provision of medical aid by evidencing the potential benefits derived from treatments and informing charitable aid. “What we learn globally will help us locally” Damania concludes.

Tidziwe Centre at Kamuzu Central Hospital, Lilongwe, Malawi (left). TATA Memorial Hospital, Mumbai, India (below).