Since its inception just over a century ago, the field of tumor virology has provided insights into the causes for many cancers. Patrick Moore, director of the Cancer Virology Program at the University of Pittsburgh, is a leading contributor to the field, having codiscovered two of the seven known human cancer-causing viruses. In 1994, with wife and collaborator Yuan Chang, Moore identified Kaposis sarcoma herpesvirus (KSHV). In 2008, the pair discovered Merkel cell polyomavirus (MCV), which can lead to the rare but extremely aggressive skin cancer Merkel cell carcinoma (MCC). Moore’s Inaugural Article (1), following his election to the National Academy of Sciences in 2012, builds on his prior MCV work by investigating how the oncoprotein MCV sT causes healthy cells to transform into cancer cells. The work determined that the MCV sT viral oncoprotein maintains a process during mitosis known as cap-dependent protein translation, a finding at odds with long-standing research on protein translation during the cell cycle.

PNAS: Although MCV is most commonly found in Merkel cell tumors, it can also be found in healthy people. What percentage of the population is thought to harbor the virus, and how do infected individuals acquire this and other cancer-causing viruses?

Moore: MCV infection is common—about 60–70% of adults have this infection, so it is part of our normal healthy viral flora. Remarkably, MCC occurs when MCV undergoes a precise series of mutations. Together with loss of immune surveillance (through immune suppression or aging), this allows unopposed expression of the viral oncogenes to drive cell proliferation. MCC is a cancer caused by mutations to our normal microbial flora rather than a host cell genome per se. This has important implications for cancer genome initiatives that may miss viral genetic contributions to cancers.

Each of the seven known cancer viruses, including MCV, is transmitted in different ways. MCV is probably transmitted through casual contact, perhaps skin-to-skin contact, mainly when we are children or adolescents. In contrast, infection with KSHV, another tumor virus in humans, is uncommon and occurs through sexual contact in the United States.

PNAS: How does MCV sT maintain cap-dependent translation, and how can this process result in cancerous tumors?

Moore: Since the 1960s, protein translation has been thought to be inhibited during mitosis—but this had not been directly measured. We found that MCV sT promotes mitosis in cells by inhibiting the mitosis-related E3 ligase [enzyme] cdc20. Rather than blocking cap-dependent translation, MCV sT paradoxically activates cap-dependent translation.

We developed a way to directly measure cap-dependent translation during mitosis, which we find is maintained in many cell lines by CDK1 [a kinase]. 4E-BP1, a key inhibitor of cap-dependent translation, is turned off in mitotic cells by CDK1, and the saturation levels of 4E-BP1 phosphorylation are higher during mitosis than at any other phase of the cell cycle. During interphase, this job is handled exclusively by mTOR [a kinase that regulates cell growth], and so it appears that interphase and mitotic cells regulate protein translation in different ways.

PNAS: Could a similar process allow other cancer-causing viruses to influence cell division?

Moore: Yes, but this may occur through entirely different pathways. KSHV, for example, is known to activate mTOR, which could be expected to induce cap-dependent translation. Other tumor viruses also activate the PI3K–Akt–mTOR pathway as well. Convergent evolution among different tumor viruses to target common pathways and cellular processes has become a long-standing source for scientific discoveries about these viruses.

PNAS: Drugs such as nocodazole may directly inhibit mitosis. Do your findings support the effectiveness and continued use of such drugs to treat Kaposis’s sarcoma, lung cancer, and many other types of cancer?

Moore: Nocodazole arrests cells in mitosis by inhibiting the mitotic spindle needed for chromosome separation. Paclitaxel is the most common cancer drug used in patients to achieve this. It is too early to say whether our findings are useful in cancer chemotherapy.

One exciting possibility is that CDK1 inhibitors might be active in cancers resistant to mTOR inhibitors. Also, combined CDK1 and mTOR inhibition might more fully block cap-dependent translation in tumors, than either drug alone. The toxicity of this approach is, of course, critical and would have to be carefully evaluated first.

PNAS: In addition to the cancer-causing viruses that you have identified, viruses have been linked to liver cancer, cervical cancer, Burkitt lymphoma, T-cell leukemia, and cancer of the nose and pharynx. Do you think the role that viruses play in many cancers has been underestimated?

Moore: It is now known that one in five cancers worldwide is unambiguously caused by infection. We are now seeing the emergence of an “epidemic” of head-and-neck cancers in the United States, probably due to sexual transmission of high-risk papillomavirus occurring decades ago. Beyond
smoking cessation, the most successful cancer prevention interventions have been the development of hepatitis B and papilloma-virus vaccines.

Cancers caused by viruses are biological accidents, just as are cancers caused by cellular mutations. Only a small fraction of people exposed to a tumor virus will develop a cancer. For example, nearly all of us have been infected for most of our lives with Epstein–Barr virus, and so, other factors—such as immunologic function or complementing mutations—determine whether or not a virus causes cancer. This seems straightforward, but it does make the origins of viral cancers complex, and cancer biologists sometimes tend to overlook them.

We also know that only a small fraction of the viruses and bacteria have been identified—in the past decade, 11 new human polyomaviruses including MCV have been discovered. We do not know if, or under what circumstances, these and other new viruses cause disease, so there certainly is potential that new infectious causes will be found for human cancers.