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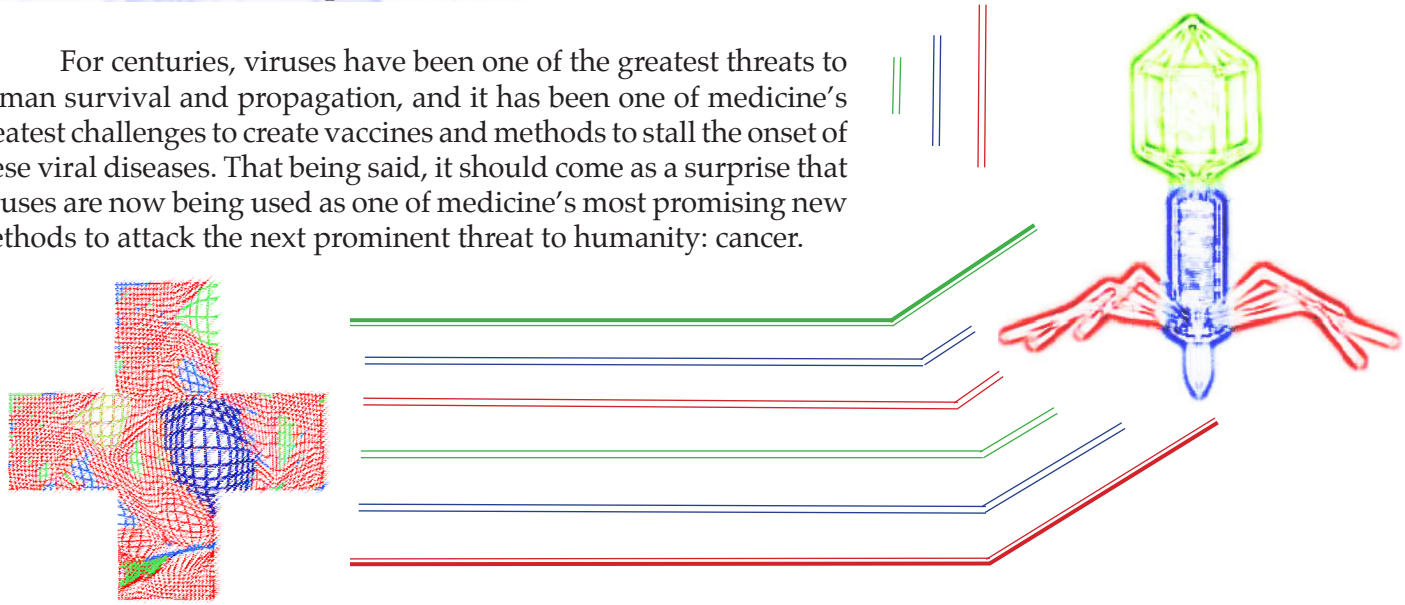
Virotherapy:

Finding New Utility in Nature's Most Dangerous Killers

Using Viruses to Combat Cancer

Andrew Taber and Alex Cheung

For centuries, viruses have been one of the greatest threats to human survival and propagation, and it has been one of medicine's greatest challenges to create vaccines and methods to stall the onset of these viral diseases. That being said, it should come as a surprise that viruses are now being used as one of medicine's most promising new methods to attack the next prominent threat to humanity: cancer.



History of Virotherapy

Since the 1800's, there have been case studies in which it was reported that cancer regression coincided significantly with viral infections. Dramatic reduction in the white blood cell count of patients (usually signifying an improving condition) was observed when the patients were infected by such viruses as influenza and chicken pox. Doctors and scientists at the time concluded that viruses, in certain environments, could temporarily improve a patient's condition, especially in young children with compromised immune systems. After many years of animal and clinical research, it was found that viral infection is indeed a very potent method to treat cancer. But, at this point scientists had to use the very blunt instrument of naturally occurring viruses in their trials, which often led to subject death. (Kelly and Russel 2007)

> "Virotherapy can succeed where past methods have failed."

The solution was to design the viruses and delivery systems using genetic engineering so that the immune system would let the viruses through and so that the viruses would target the desired cell type. The tools needed to achieve this goal, however, were not developed until relatively recently. Until then, science used a method called targeted evolution to encourage the propagation of mutations that would result in viruses attacking cancer cells.When recombinant DNA technology was developed, the effectiveness of virotherapy could be even more directly controlled. Today, virotherapy is showing significant effectiveness in treating many cancers and diseases in mice, and trials have even shown improvements in treating advanced melanoma in humans (Nutting 2005).

These results are too significant to be ignored, and scientists are wasting no time in developing new viruses to fight other diseases. One of the ways to solve the problems of cell targeting is to add cancer-specific binding proteins to the virus. Each type of cell has an outer membrane that acts as a selective barrier between the cell and its surroundings. All membranes are coated with proteins that are used to identify a cell and its purpose in the body. One way of thinking of these proteins is as nametags, and scientists' job is to engineer these proteins so that viruses "know" where

in the body to inactivate the innate function of cells and reproduce within them. Now that our knowledge of genetics has improved and we know that every type of cell has its own genetic marker, we can design a virus to look for the exact cell type we want it to: the cancer cell (Thirukkumaran and Morris 2009).

Advantages and Disadvantages to Virotherapy

The specificity of oncolytic vectors (cancer-killing viruses) was shown by Dr. Ryan Cawood of the University of Oxford and his colleagues. In his experiment with adenovirus, Cawood was able to show that cancerous cells lack a defense mechanism that healthy cells have to prevent infection. The other highlight of this research is that the viruses used in oncolytic technology can be highly infective of cancer cells with minimal risk to infect other healthy cells (Cadwood 2009).

After they infect the cancer cells they have two potential methods of killing the cells. The first way involves viruses that are engineered to contain the specific anti-cancer drugs or radioactive substances to deliver a precise amount of radiation or drugs to kill the cancer cells. Another method, which this paper will focus on, is to use the innate ability of viruses to kill cells.

When a virus infects a cell, it hijacks the cell's production system and forces the cell to make copies of the virus. Eventually the cell makes so many copies that the viruses overfills the cell and bursts through the cell membrane. Imagine overfilling a balloon with air and bursting it; this is the type violent death, called lysing, that cells undergo when infected by viruses.

When contrasted with more traditional forms of cancer treatments, virotherapy is much safer and more efficient (Thorne, Negrin, and Contag 2006). Radiotherapy and chemotherapy, which use blankets of energy to destroy the cancer cells, are extremely painful and have long-lasting side effects. Essentially, these treatments are poisoning the body, hoping to poison the cancerous regions and annihilate the tumor before the body itself is destroyed. Nearby healthy cells are destroyed, and the side effects can cause further complications in overall health. Though the methods have improved in these treatments, they are still essentially primitive and are wildly expensive. Surgery, another option, is just as imprecise, and can also incur the dangers of infection and bodily stress. Virotherapy can succeed where these methods have failed.

However, with any new miracle cure in medicine, there is and always should be skepticism. The lack of comprehensive results

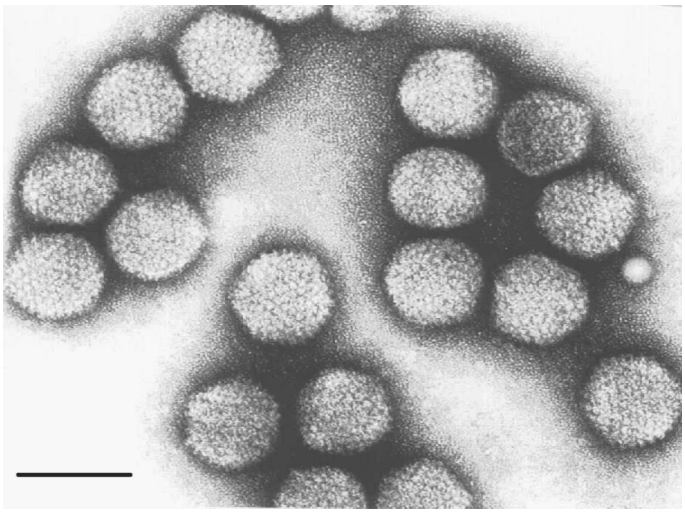


Figure 3. Human adenovirus.

in human trials justifiably leads some to question the safety and efficacy of such methods. Especially when considering potentially dangerous viruses being used as oncolytic vectors, the safety of healthy tissue is a concern, since cell targeting is not perfect, and the vectors must still be kept virulent in the body to properly function. Furthermore, the ethical impact present in any discussion of bioengineering must also be considered, such as the epidemiological risks of virus mutations or the spread of the oncolytic viruses to the greater population.

The research in virotherapy that is being conducted now carries with it the hope of many cancer patients. With proper and thorough research, it is possible that virotherapy could be the next mainstay of medicine, like vaccinations and penicillin before that. One of the most promising studies, by Dr. Xue Qing Lun of the Tom Baker Cancer Center and his colleagues, showed that the myxoma virus, a virus that causes skin tumors in rabbits, has the ability in mice to fight cancers cells that have been grafted with human cancer cells. In fact, the results are so significant that this treatment with the oncolytic myxoma virus almost doubled the life expectancy of the cancer-afflicted mice. Even more surprisingly, three out of the

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five mice that were slated to die lived past their life expectancy with this treatment and were essentially "cured" of their cancer (Lun et al. 2007).

Virotherapy could very well hold the secret to treating many varieties of cancer economically and selectively. The potential for pharmacological applications in large-scale manufacturing would be irresistible to pharmaceutical companies, which should spur industry investment and advances in the field. If industry could develop and mass produce virotherapeutic tools, we may see a dramatic decrease in the cost of cancer treatment. Now, the most dangerous pathogens of human history are being used to defeat one of modern medicine's most evasive and pernicious threats.

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