

The Development of the Anti-Viral Compound Pleconaril

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The Ehrlich award is not only an exceptional honor, but it is especially meaningful to me because I was born in Frankfurt, where I experienced my first three and a half years of schooling. Among my memories is one of my grandmother telling me about her widowed friend whose husband had discovered a drug called Salvarsan. Clearly, in retrospect, my grandmother was telling me about the widow of Paul Ehrlich. However those were not happy days. Pupils and teachers alike persistently harassed me, on account of my Jewish mother, which made school learning difficult. Every day was filled with terror until my mother was able to arrange for me to go to a boarding school in Holland at the tender age of eight years. Fortunately we were able to immigrate to England just one month before the start of the Second World War, where at last I felt save. It is, therefore, of very special significance to me to return to Frankfurt and to be here in the Paulskirche (through which I had frequently wandered with my mother who loved Frankfurt and wrote illustrated articles for the Frankfurter Zeitung's Stadtblatt), together with my colleague and friend, Steve Harrison, in order to be presented the Ehrlich award.

It has been known since the 1930's, as a result of the pioneering work of Stanley, Bernal, Fankuchen, Crowfoot-Hodgkin and others, that viruses could be crystallized much like common salt. Furthermore virus crystals could be dissolved and used for infecting cells and the production of infectious progeny virus. However, crystals can be probed with X-rays to determine their three dimensional atomic organization. During much of the 20th century X-ray crystallography made steady advances. In the late 50's I was part of Max Perutz's team that determined the structure of the first proteins. The obvious next challenge was the structure of a whole virus, both because of the biological significance of an object that was close to being an independent living entity and because of the technical challenge of such an endeavor. After decades of effort Steve Harrison and his colleagues were the first to determine the structure of a small spherical plant virus in 1978. We were able to do the same a year later studying another plant virus. To everybody's amazement these two viruses had remarkably similar structures, demonstrating that they almost certainly must have arisen from a common primordial ancestor.

With this success, I decided that it was time to study an animal virus. This required that we propagate virus in cell culture, a process far more difficult and tedious than growing plant viruses on tomato or bean plants. I was fortunate in being able to persuade my home institution, Purdue University, to give me funds for establishing a cell culture laboratory. I was also fortunate in obtaining help, encouragement and sound advice from Roland Rueckert of the University of Wisconsin. Thus in 1985 we were able to announce the structure determination of the first animal virus, namely that of a human common cold virus. Remarkably it also had a structure that strongly suggested the same evolutionary origin as the earlier studied plant viruses. But this structure was also

extraordinarily informative of the biological processes by which the virus entered cells, protected itself from host immune surveillance, and self assembled newly synthesized components into infectious particles.

I remember clearly the day in April 1985 when we first saw the principal features of human rhino virus serotype 14 (HRV14). It immediately struck me that there was a large surface fissure, which I came to name "canyon", a comparison with Arizona's Grand Canyon. I equally remember the day, a couple of weeks later, when Roland Rueckert and Barbara Sherry came down from Wisconsin, to plot their newly determined amino acid mutations onto our new map of HRV14. These mutations located the binding sites of neutralizing antibodies. We found that these sites were on the viral surface around the canyon's rim. Possibly, I argued, the viral receptor would be able to bind into the canyon avoiding the surface sites available to antibody binding. This idea has become known as the "canyon hypothesis", which we showed, in 1993, to be a valid prediction of the receptor binding site in many rhino as well as entero viruses.

I had heard that Mark McKinlay, Guy Diana and others at the Sterling Winthrop Co in New York had been developing a set of compounds able to inhibit rhino virus propagation in cell culture. Tom Smith, a new post-doctoral fellow in my laboratory in 1985, proceeded to show that the target for these compounds was the viral capsid and that their site of binding was a hydrophobic pocket underneath the canyon. The compounds were found to inhibit viral attachment, probably by competing with receptor attachment. These compounds were also shown to stabilize the virus as a result of their complementarity of shape and hydrophobicity within the pocket. Normally the pocket is filled by a cellular, probably lipid, "pocket factor", which regulates viral stability. The virus is essentially inert when the pocket factor is bound while being transmitted from host to host, but, when the virus recognizes a cellular receptor, the pocket factor is expelled by the competing host receptor, thus destabilizing the virus and thus allowing the viral genome to enter the cell's cytoplasm. Thus the action of the anti-viral compounds is to interfere with the normal regulating function of the pocket factor.

Knowledge of the shape and chemical properties of the anti-viral compounds' binding site, plus requirements for structural stability, helped Guy Diana and his group of chemists to synthesize Pleconaril (VP 63843). This compound, a derivative of earlier studied compounds, has undergone extensive phase 1, 2 and 3 clinical tests. It has already saved the lives of at least 100 patients who were infected with rare but lethal entero viruses and is likely to be approved shortly by the US FDA as an anti-rhinovirus agent.

I thank the Paul Ehrlich Foundation for giving me the honor and pleasure to receive the Ehrlich prize in recognition of the work I have here described briefly.