More than 40 million people have died from influenza in the past 100 years. Control of the virus has remained elusive, because it is constantly mutating into new strains: the immune system may develop anti-bodies to one strain, but the antibodies don't recognise the new strain and so people can be reinfected. Many virologists fear that it is only a matter of time before a mutation leads to a particularly virulent and deadly strain, such as the one that killed some 20 million people in 1919.

In one of CSIRO's most excellent and internationally recognised scientific works, Dr Peter Colman led a research effort that established the 3D structure of the neuraminidase protein on the flu virus, and identified a site on the surface of the virus that did not mutate. This provided a target for a drug against the virus and chemists led by Dr Mark von Itztein at Monash University's College of Pharmacy were able to synthesise a drug that locks onto this site and blocks the virus from leaving a cell. This prevents it from spreading to other cells. The work was recognised in the 1995 Australia Prize.

The development of the drug was backed by Biota Holdings, who licenced it to the multi-national pharmaceutical company, Glaxo-Wellcome. The drug has now been successfully trialled on human volunteers and is set to be launched commercially in 1998. The market is estimated at over $1 billion and its progress has attracted international interest in the developing Australian biomedical research capability.

The flu drug: start-up company plays crucial role

Dr Peter Colman's Australia Prize-winning work on the development of a drug to treat all forms of the influenza virus is now well on the way to its commercial launch, scheduled for 1998. The launch will come 15 years after Dr Colman began advocating the idea of an anti-viral drug that targets the neuraminidase protein on the surface of the influenza virus.

During these years, Dr Colman led a multi-disciplinary research effort to overcome fundamental scientific barriers to his concept of a drug designed on the basis of the structure of the virus. At the same time, he served as Director of a start-up company that secured finance for the research. The company had a roller coaster ride in the financial markets before research results won the interest and support of Glaxo. Glaxo's support provided access to the massive development capital needed to bring the drug to the market.

Project origins

Dr Colman first became interested in the flu virus in 1977, when he was at the University of Sydney, doing research on the structure of antibodies. The following year, he moved to the Division of Protein Chemistry at CSIRO, where he teamed up with Dr Jose Varghese and initially continued this line of research. "It was one of those stories familiar to most scientists, where you start out to do one thing and ended

up doing something else," he recalls. "I was fascinated by the immune system and how antibodies could detect and bind to viruses. We started looking at how one strain of influenza differed from another, with the aim of identifying how different the virus had to be, before it could elude the antibodies and reinfect."

In the course of this work Dr Colman, in collaboration with Dr Graeme Laver of the Australian National University, was able to establish details of the 3D structure of the neuraminidase protein on the flu virus and observe the changes that occurred when the virus mutated into a new strain. "We found that the changes in the protein were dramatic – so much so that we couldn't help but be drawn to the fact that about the only part that didn't change was this one small part on the surface of the neuraminidase."

It was this work that led Dr Colman to advocate targeting the neuraminidase protein with an anti-viral drug. "It wasn't a new idea," he said. "People had tried to make inhibitors of neuraminidase in the 60's and 70's without success, and so by the 80's it was regarded as a dead end. But our structural work showed just how invariant this site was and I was convinced that this was the place to put pressure on the virus."

Dr Colman pushed his ideas at a conference in London in 1983 to mark the 50th anniversary of the discovery of the influenza virus. His talk drew the attention of Glaxo. The pharmaceutical giant showed some interest, but twelve months of negotiation did not yield a research agreement. "It was hard to sell them on the idea of collaborating with researchers in the southern hemisphere in a field of research that most people didn't believe was going anywhere" he recalls.

It was at this time that CSIRO's support was crucial. "CSIRO provided the institutional support and the resources to pursue our ideas and develop some strategic science and intellectual property. I couldn't have equipped the laboratory we needed if we had been relying on NH&MRC grants. Successive Chiefs at my Division kept backing us, even though there were many who said that the science wasn't right."

Early commercial structure

Dr Colman says the move into what was a commercially oriented field of research happened unremarkably. "I was always interested in medical applications, and I moved into this field because I was fascinated by whether it was scientifically possible to design an inhibitor based on knowledge of structure, which hadn't been done for anti-virals.

"We also continued with some work that didn't lead to commercial applications. In 1987, we were on the front cover of *Nature* magazine with the first ever picture of an antibody attached to a viral antigen. This led to quite heretical ideas about how antibodies could change their shape when binding to antigens. Scientifically, this was as big as the work on the drug."

When discussions with Glaxo broke down in the mid 80's, the door opened for a local entrepreneur, Mark Crosling. Crosling had previously been in discussion with the then Division of Protein Chemistry about raising funds for other areas of research.

Crosling formed a company, Biota Ltd, and raised an initial $3 million from a sharemarket float in 1986 to back the development of the flu drug.

Dr Colman: “I knew that we’d eventually need one of the large pharmaceutical companies to bring the drug to the market. The costs of upwards of $100 million to go through the trials and to set up a manufacturing facility were simply prohibitive to anyone else. But for the moment, Biota offered an important route to bring in the research funds we needed. CSIRO was under pressure to find external earnings and so this was the best opportunity for us at the time.”

Dr Colman, with CSIRO’s agreement, became a Director of Biota and allowed his name to be used in the company prospectus. “In effect, I became the Research Director of the company,” said Dr Colman. “This was both positive and negative. I had the confidence of the Board, who backed my judgement and let me run the research without interference. But the downside was that, the company started to expect free scientific advice. When they get legal or accounting advice they pay for it. But for scientific advice, which is even more fundamental, they weren’t accustomed to paying. Directors really should be making judgements about strategy and company performance, rather than acting as unpaid advisers. I wouldn’t encourage that arrangement to other CSIRO staff.”

Biota initially backed three projects, of which only the drug design progressed. The company raised an additional $2 million from the Government’s Industrial Research & Development grants scheme and the discretionary grants scheme. “These funds were crucial,” said Dr Colman. “For example, edible birds nest was the best starting material for the compounds we wanted to make, but it couldn’t be imported because of quarantine restrictions. So we had to synthesise starting material and the IR&D Board funded our chemists to develop enzymatic methods for creating what we needed. Getting those grants involved a lot of work, especially for the company.”

The chemists working with Dr Colman came form the Victorian College of Pharmacy, almost next door to Dr Colman’s Division at Melbourne’s Parkville strip. The College is now part of Monash University. “We started working with the Pharmacy College because of the enthusiasm, energy and entrepreneurship of the then Dean of Medicinal Chemistry, Peter Andrews. On reflection, we could have worked with chemists from within CSIRO. But the physical proximity of the College was a telling factor.”

Creative freedom for multi-disciplinary researchers

Dr Colman’s approach to managing the research emphasised giving the individual researchers creative freedom. “We had an overriding objective which everyone knew and supported. But we were pursuing very fundamental science, even though we had an application in mind. No-one had done anything like it before, so it wasn’t really sensible to set timelines and have Gant charts and the like. Nowadays, I could confidently predict that for a known structure, it should be possible to conceive and synthesise an inhibitor within six months if all went well. But at that time, we had no idea whether it would work at all. We didn’t even know why attempts failed in the 60’s and 70’s to find inhibitors that targeted neuraminidase.”

"What we all signed on to was to give maximum effort rather than to deliver specific outcomes within a set time frame. The key need was to keep staff enthusiastic and owning their effort. Asking them to put in the long hours and creative thought meant trusting them to get on with the job and not looking over their shoulder all the time."

"It was also a multi-disciplinary effort. I was fortunate to have encountered different disciplines when, having trained as a physicist, I moved into protein crystallography and research on antibodies. But I didn't try to prescribe what the chemists, for example, should do. There were many constraints in synthesising the possible inhibitors, including whether a particular chemical had any prospect of being manufactured on a commercial scale. The chemists were best placed to weigh up those factors."

Nevertheless, Dr Colman did keep his finger firmly on the pulse of research progress. For the first three to four years, he went into the Pharmacy College every Friday afternoon to talk with the chemists about what was being done and why. This meant that research directions were being constantly re-evaluated and updated in the light of developments. A certain amount of formal research planning also had to be done for inclusion in the applications for Government grants. Reports on developments and research directions also had to be prepared for the monthly Biota board meetings.

Trial-stage strategy

Dr Colman remained a Director of Biota until 1992, when the main research phase concluded with the drug having been conceived, synthesised and shown to be active. The emphasis then shifted to trials of the drug. At Biota, he encountered many of the usual difficulties of start-up companies. As with the science, he attributes his success to keeping himself informed of the company's situation, being prepared to contribute and comment on its development, but allowing the commercial people to get on with the job.

"I decided that if the commercial or development strategy proved wrong, I could go down Collins Street and admit to errors of judgement. But what I wasn't prepared to allow was any weakness in the science, because that was my core professional responsibility to both the company and to my own standing as a scientist."

The sharemarket crash of 1987 took the share price of Biota down with it. This didn't affect the cash position of the company but it did make it vulnerable to predatory takeovers. Dr Colman avoided becoming involved in the manoeuvrings during the two boardroom battles that eventuated. "I kept my focus on the science. I made it clear that I was comfortable with the existing Board. Things were proceeding well and I didn't see any additional value to the project, or to CSIRO, in making a change."

The project also had to contend with a scientific split. Dr Graeme Laver of the Australian National University moved on to work with another team. His role was taken up by CSIRO staff, which put added pressure on resources.

Dr Colman believes that the commercialisation strategy pursued by Biota was a good one. When they were ready to trial the compound, they approached Glaxo to run them, but didn't give away any rights at that stage. When the compound was demonstrated to be active, the company then gave presentations to the top six global pharmaceutical companies. Dr Colman assisted these presentations.

"This time, we had some real intellectual property to get their attention and some leverage over where subsequent work would be done," he recalls. Glaxo eventually came up with the best commercial proposal and Biota entered into an agreement with them to trial the drug and eventually market it.

Dr Colman is now Director of the Biomolecular Research Institute, a body set up by CSIRO and the Victorian Government's Strategic Research Foundation. He says he's willing to go down the start-up company route if it seems appropriate. "I'm doing it again in another area at the moment," he explains, "although, unlike Biota, the company isn't listed publicly."

He says that the big issue in commercialising research, no matter how it's structured is the timing of bringing in a commercial partner. "If you bring in even an Australian company at too early a stage, before you have some intellectual property secured, you have very little bargaining power over how and where the final product is taken to the market. I firmly believe that public research organisations must nurture their strategic base and be prepared to back their researchers in the early stages, without external funds and without excessive demands for plans and reports. On the other hand, to get anything applied, you have to raise money and commercial interest. That means eventually creating a sound business case. As scientists, we sometimes underestimate the effort the commercial people have to put into that, and the information they need," he said.