Research Update

Homing in on cause of bone tumours

A serendipitous discovery by researchers at the University of British Columbia's Canadian Genetic Diseases Network may bring scientists a step closer to preventing hereditary multiple exostoses (HME), a condition that causes about 15% of all bone tumours in children.

Dr. Frank Tufaro and his colleagues searched about 100 000 human gene sequences and to their surprise found that 1 gene that affected the expression of cell surface molecules — *EXT1* — had already been identified (*Nature Genet* 1998;19:110-1). *EXT1*, a member of the EXT gene family, produces a protein localized to the rough endoplasmic reticulum. It is essential for controlling cell surface glycosaminoglycans (GAGS), which in turn may influence the binding of "Hedgehog proteins." One variety of these proteins, the "Indian hedgehog," is already known to be critical for regulating bone development in humans. An absence of GAGS could therefore alter bone growth. It appears that inactivation of one EXT gene results in formation of an exostosis — a benign bone growth — while inactivation of another EXT gene could result in malignant changes in bone cells.

"Nobody ever knew that there was a link between the gene known to be involved in tumour formation and GAGS," says Tufaro. The discovery is significant because, of the 12 tumour-suppressor genes discovered so far, *EXT1* is the first to be "found in that pathway," says Tufaro. Shortly after Tufaro's discovery was published, EXT was also found to play a critical role in development in the fruit fly by binding to its hedgehog gene.

In humans, testing of DNA isolated from surgically removed tumours shows that GAGS are defective in tumours. Tufaro's group is now looking at what enzymatic function the *EXT1* gene plays and at which growth factors are missing. The disturbance of GAGS in other kinds of tumours, such as brain and colorectal tumours, "may be an essential event," says Tufaro. "If you are missing it, you may get tumours." — © *Heather Kent*

Breakthrough in fighting flu

A new group of drugs, neuraminidase inhibitors, is being heralded as the first important discovery in anti-influenza medications in 25 years. Zanamivir, one of the new, selective neuraminidase inhibitors, has shown promise in preventing and treating influenza in a multinational clinical trial (*N Engl J Med* 1997; 337:874-80).

"For physicians, this group of drugs has the potential to advance the management of influenza in individuals quite considerably," says Dr. Fred Aoki, professor of medicine at the University of Manitoba and principal Canadian investigator in the clinical trial. "Zanamivir has the potential to provide physicians and their patients with something better than symptom treatment provided by, for example, Aspirin, acetaminophen and decongestants. It likely will be better than amantadine, which is the only antiflu drug currently on the Canadian market."

Unlike amantadine, which inhibits only influenza A virus strains, zanamivir inhibits both influenza A and B. The new drug also appears to be better tolerated than amantadine and does not engender the emergence of drug-resistant viruses, which appear within 3 to 5 days with amantadine, limiting its usefulness. "In addition to hastening recovery from influenza, zanamivir recipients visited the doctor less often and were back at work faster," Aoki said.

Zanamivir is inhaled into the lungs as a powder. A second neuraminidase inhibitor, taken as a tablet, also has entered clinical trials. "The neuraminidase inhibitors will not be a substitute for vaccine," Aoki notes. "As such, they will likely have a greater role in maintaining and restoring individual health than in public health. Finally, our enthusiasm must be tempered by the fact that few data are available on whether zanamivir works in the high-risk population with influenza, such as those with heart disease, kidney disease, diabetes, etc."

The group of drugs to which zanamivir belongs was developed as a result of Australian research in which computer techniques were used to design molecules to block the neuraminidase enzyme. Neuraminidase is known to be important in the multiplication of the influenza virus and the development of disease; it is also known that antibodies against this enzyme help reduce the severity of disease. The Australian researchers crystallized the enzyme and, using x-ray diffraction technology, were able to manufacture molecules to fit in the enzyme's "pocket," thus blocking the enzyme and preventing the virus from replicating and causing disease. An application to market zanamivir in Canada has been filed. — © *Jane Stewart*