reduction in total Aβ levels and a reduction in plaque surface area (Bush, A. *et al.*, http://www.sfn.org/).

Clinical studies

PBT1 is now in Phase II clinical trials in 50 patients with mild-to-moderate AD at the Health Research Institute of Victoria and the University of Melbourne. So far, 15 patients have been recruited to the 6-month study that is expected to report results in about a year's time. Results from earlier studies are expected to be submitted for publication in early 2001.

Most (80%) Aβ in the brain is present in an insoluble, diffuse form, a further 2% being soluble. The rest is in plaques. 'We are targeting the soluble and diffuse deposits and are indifferent to the plaque deposits, although they do seem to be reduced with treatment,' says Bush. He believes that this approach has advantages over others, such as blockade of the secretase enzyme involved in Aβ deposition and immunological approaches, in that it effectively leaves Aβ alone; 'We do not assume that Aβ is of no use,' he says.

PBT1 is targeted at the brain and therefore should not affect copper and ion levels in the rest of the body. Carol A. Scorer, Head, Alzheimer's Disease Research at GlaxoWellcome (Stevenage, UK) will be interested to see if metal chelation in the brain proves to be safe and tolerable, given the need for tight homeostatic regulation of metal ion levels in the body. In light of the evidence that Aβ trapped in plaques appears to be less toxic than the soluble or diffuse form of the protein, she also questions the safety of dissolving the plaques and releasing Aβ: 'It is possible that it could be harmful to solubilize a large quantity of deposited amyloid within the brain,' says Scorer. 'The key issue will be whether the solubilized amyloid is rapidly and harmlessly cleared,' she adds. This is a question that presumably will be answered in forthcoming publications from the research group.

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Immunization blocks gastrin's ability to promote tumour cell division

Kathryn Senior, Freelance writer

A novel immunotherapy to target gastrointestinal cancers has now reached Phase III clinical trials. Patients with Stages III and IV pancreatic cancer and Stage IV stomach cancer are currently being recruited to test a vaccine-like therapy that blocks the action of gastrin. In the UK/Europe multicentre trial, the Phase III study will compare the anti-G17 immunogen, developed and produced by Aphton Corporation (Miami, FL, USA) with gemcitabine, the best chemotherapeutic agent available for pancreatic cancer. In the US-based trial, anti-G17 will be given in combination with gemcitabine and compared with a group receiving gemcitabine only, both for ethical reasons (gemcitabine is the approved drug for pancreatic cancer in the US) and to investigate a possible synergy between the two treatments.

Gastrin as a growth factor

During the past 10–15 years, gastrin has been identified as the central trophic factor for gastrointestinal cancers and has therefore emerged as a potential anticancer target. There are several forms of gastrin; the precursor molecule preprogastrin is cleaved by an endopeptidase to progastrin, which is further processed to glycine-extended gastrin 34 and to

gastrin 34. These 35- and 34-amino acid peptides can be cleaved to form glycine-extended gastrin 17 and gastrin 17, respectively. Cells with gastrin receptors can respond to mature amidated forms

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of gastrin, as well as precursor forms, particularly glycine-extended gastrin 17.

'It has become clear that in cancer cells originating in various parts of the gut (from the oesophagus to the stomach, pancreas, liver, colon and rectum) the gastrin gene and the genes that encode the gastrin receptors are switched on at a very early stage of oncogenesis,' explains Phil Gevas, CEO at Aphton. Basal-level serum gastrin and gastrin produced normally in response to eating can stimulate tumour growth, although a significant proportion of gastric tumour cells also produce gastrin that acts locally via an autocrine pathway to further promote cell division. 'Gastrin and its precursors are potent growth factors,' comments Martyn Caplin (Royal Free Hospital, London, UK), whose group has just demonstrated that the gastrin receptor and gastrin precursors, absent in normal pancreatic tissue, are produced in pancreatic cancer cells in most patients[1].

Strategies to inhibit gastrin production

As the importance of gastrin as a growth factor became clear, researchers have investigated inhibitors of gastrin production. Gastrin-receptor antagonists have been evaluated, but proglumide, the only compound evaluated in clinical trials, failed to produce any survival benefit in a Phase II trial[2]. Preclinical work demonstrated that anti-gastrin antibodies bind to gastrin peptides preventing their interaction with gastrin receptors and *in vivo* animal studies showed that infusion of anti-gastrin antibodies could inhibit the growth of human colorectal xenografts[3].

However, passive infusions of either polyclonal antisera or monoclonal antibodies have serious drawbacks for the patient. 'Antibodies given passively to patients are not long-lasting and a 1 or 2-h infusion would be required every week,' says Gevas.

Over 10 years ago, the research team at Aphton decided that active immunization was likely to work better. A segment of gastrin 17, consisting of the 9-amino acid stretch at the amino-terminal end of the molecule, was chosen as an immunogen, and was linked via a peptide spacer to diphtheria toxoid to induce immunogenicity. Preliminary studies in nude mice and rat tumour models as well as in Phase I human trials[4] showed a high antibody response that lasted at least 6 months. Sue Watson (University of Nottingham, UK) highlights that the antigen epitope used in anti-G17 is unique to gastrin 17. 'After priming injections, antibody titres are raised sufficiently to mop up tumour-associated gastrin molecules as well as all serum gastrin 17 and gly-extended gastrin 17,' she explains. The antibodies elicited bind to the N-terminal end of the gastrin 17 molecule, but effectively engulf the whole peptide, preventing the C-terminal end binding to the gastrin receptor on cells.

An anti-gastrin 'vaccine'

Anti-G17 has shown good preclinical trial results, which are detailed in a recent review[5]. 'One of the most interesting studies shows that, in a mouse model of colorectal cancer progression, animals given a standard proton pump inhibitor were pushed further and faster towards malignancy. However, when anti-G17 was also given, the progression towards malignancy was slowed significantly,' Watson explains. This has obvious implications for patients with acid reflux or stomach ulcers who are prescribed proton pump inhibitors. 'These drugs are known to increase gastrin secretion significantly; if patients also have colonic polyps, such treatments, particularly if given long term, could pose an increased risk of both colon and oesophageal cancer,' says Watson.

'This is a nice piece of work that also raises the possibility that this immunogen could be used outside oncology for patients with conditions such as atrophic gastritis, Zollinger-Ellison Syndrome and pernicious anaemia,' points out Caplin.

Future studies

Phase I/II trials of anti-G17 suggest that the immunogen is safe and effective. In one trial in patients with advanced colon cancer, excess gastrin antibodies were induced in 95% of patients and median survival was 338 days, compared with 184 days in matched controls. Although Phase III trials will be in patients with advanced cancers, Gevas confirms that after FDA approval is gained, Aphton intends to explore other indications for the drug. 'These could include its use in earlier stage cancers and, eventually, its prophylactic use in patients with hypergastrinaemia or those with a genetic predisposition to colon cancer,' he predicts.

Although delighted with the progress of anti-G17, Gevas is cautious about describing it as 'a cancer vaccine'. Many workers around the world are developing so-called 'cancer vaccines' that target key molecules on the surface of the cancer cell to attempt to destroy it, he says. 'Our immunogen cuts off the cells' supply of one of the primary growth factors that fuels the process of malignancy,' he says. Hopefully, it will slow cancer growth and perhaps, in combination with chemotherapy, produce an enhanced degree of tumour cell-death, but whether this will then allow the body's defences to destroy and eliminate the tumour cells will require a great deal of further work,' he concludes.

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