Angel believes that DPb99 is effective for long periods after the initial ischaemic event because of its specific mechanism of action. 'The target is the penumbra, a zone that is suffering but not yet dead. Blocking the calcium-induced apoptosis and reducing the immediate consequences of calcium-induced depolarization hinders the propagation of neuronal death and gives us a wider therapeutic window.'

### Safety studies

D-Pharm has just finished the two phases of the Phase I safety assessment of DPb99 using 0.03–1.00 mg $kg^{-1}$ in single and repeated doses in young and elderly healthy male volunteers. 'We were particularly happy that we saw no cardiovascular effects on ECGs, nor effects on blood pressure and heart rate. The only major side effects observed were reactions at the sites of injection,' says Angel. A Phase II study is currently being planned to begin shortly in stroke patients.

### Future studies

Other studies currently being undertaken include investigations whereby DPb99 not only reduces calcium levels at the vicinity of the cellular membrane but replenishes calcium stores when these are depleted.

D-Pharm is developing its Membrane-Activated Chelator (MAC) platform to create additional compounds that could be used for other chronic diseases. 'Copper, iron and zinc ions are all thought to play important roles in chronic neurodegenerative disorders, such as Parkinson's and Alzheimer's disease. We are currently investigating additional MAC compounds in animal models of these diseases.'

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*Janet Fricker*

# Dietary supplement to treat asthma

Scientists at Pilot Therapeutics (Winston-Salem, NC, USA) have developed a dietary supplement to inhibit the production of leukotriene $B_4$ ($LTB_4$), one of the key mediators of inflammation in asthma. The main constituents of the supplement are the (*n*-6)-series fatty acid γ-linolenic acid (GLA), which is mostly found in the oils of evening primrose and borage seeds, and the (*n*-3)-series eicosapentaenoic acid (EPA), an inhibitor of the enzyme Δ-5-desaturase, which is involved in the production of arachidonic acid from fatty acids such as GLA (Ref. 1).

Leukotrienes such as $LTB_4$, $LTC_4$ and $LTD_4$ are produced from essential fatty acids via the metabolism of arachidonic acid through the lipoxygenase metabolic pathway, and are known to play an important role in the asthmatic response. $LTB_4$, for example, is released by activated mast cells and macrophages and acts as a chemoattractant to neutrophils and eosinophils, which cause airway inflammation. In theory, as the quantity of $LTB_4$ produced in the inflammatory cells of people taking GLA is reduced, the fatty acid could be a useful adjunct to inhaled asthma therapy[1]. Moreover, GLA has already been shown to relieve the signs and symptoms of other inflammatory conditions such as rheumatoid arthritis and ulcerative colitis[2].

### GLA – the paradox

The ability of GLA to reduce inflammation is paradoxical because it is also a potential metabolic precursor of arachidonic acid, which itself is transformed in the liver into leukotrienes and prostaglandins. Therefore, says Floyd Chilton, Chief Scientific Officer of Pilot Therapeutics, 'Given alone, GLA causes an increase in serum arachidonic acid resulting in an attenuation of its anti-inflammatory activity and, more importantly, potential cardiovascular adverse effects via the formation of platelet-aggregating endoperoxides and thromboxanes.'

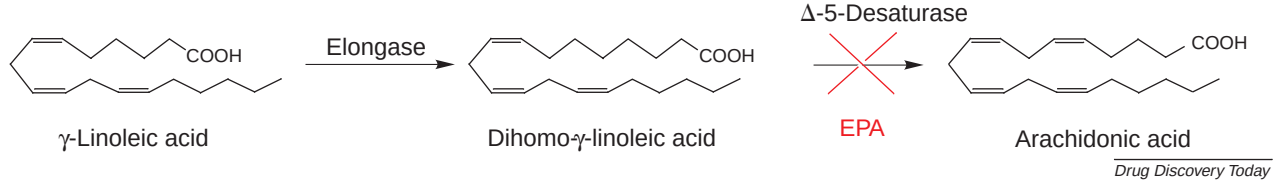


***Figure 1.*** *The Δ-5-desaturase inhibitor, eicosapentaenoic acid (EPA), inhibits the increase in arachidonic acid levels caused by the dietary supplement, γ-linolenic acid (GLA).*


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Chilton and colleagues hope that they have overcome this problem by combining GLA with the Δ-5-desaturase inhibitor, EPA. The two-step production of arachidonic acid in the liver from GLA requires the molecule to be first elongated to produce the structural analogue of arachidonic acid, dihomo-γ-linolenic acid (DGLA), and then desaturated by Δ-5-desaturase (Fig. 1)[1]. However, immune cells such as neutrophils do not contain Δ-5-desaturase and consumption of high quantities of GLA therefore leads to a build-up of DGLA in these cells[2]. 'This fatty acid competes with arachidonic acid resulting in an inhibition of the synthesis of the important inflammatory mediators such as $LTB_4$', explains Chilton. Anti-inflammatory metabolites, including the cyclooxygenase product prostaglandin $E_1$, are also generated from DGLA (Ref. 2).

### Early studies

Studies in human hepatocarcinoma cells (HepG2) – a model for investigating fatty-acid metabolism in the liver – confirm that EPA inhibits Δ-5-desaturase and causes a build-up of DGLA, thus inhibiting the increase in arachidonic acid levels[1]. Studies in volunteers taking a combination of GLA and EPA also show that EPA prevents a build-up of arachidonic acid in the serum. Moreover, in the presence of EPA, DGLA builds up in immune cells without an accompanying build-up of arachidonic acid from the liver, thus maximizing the anti-inflammatory effects of GLA without the adverse effects associated with increased production of arachidonic acid[1,2].

'More recently, our work has addressed the minimal daily dosage of GLA required to obtain a maximum benefit as well as the contribution that other dietary fatty acids with proven anti-inflammatory action might have on these indices of inflammation,' explains Chilton. 'Another trial identified the minimal effective dose of (*n*-3) fatty acids. This dose will define concentrations in the final product,' he adds.

### Studies in asthma

The next step will be to test the safety and efficacy of different dosages of the fatty-acid combination in people with asthma; 'a forthcoming trial in people with asthma will evaluate the effect of the product on key biomarkers of lung inflammation,' explains Chilton.

The safety consequences of dietary supplements are of crucial importance and are exemplified in the potential cardiovascular risks of taking GLA alone. Indeed, Chilton and colleagues highlight this point in their recent study: 'As the nutraceutical industry continues to experience explosive growth, it will be increasingly important to understand the safety profiles of dietary supplements'[1]. If Pilot's studies are successful, Chilton anticipates that the supplement will be available early in 2001.

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*Sharon Dorrell*

# News in brief

### Autoimmune diseases committee to sit within NIH Director's Office

An Autoimmune Disease Coordinating Committee is to be created to sit permanently within the Director's Office of the National Institutes of Health (NIH), reported the American Autoimmune Related Diseases Association (AARDA) recently. The committee, created by legislation that is part of the Children's Health Act, will oversee all autoimmune research carried out by NIH facilities and will co-ordinate these activities with other relevant Federal agencies, such as the Centers for Disease Control and Prevention and the Food and Drug Administration.

The diseases of the autoimmune process are highly diverse (type 1 diabetes, lupus and multiple sclerosis) and it is hoped that effective coordination of research and knowledge will yield improved results and new ways to secure funding. One of the major questions to be addressed is why autoimmune diseases disproportionately affect women as autoimmunity is one of the ten leading causes of death among women aged 65 and under. Other research will examine the biomedical, psychosocial and rehabilitative issues associated with these diseases.

### Public would prefer to know if genetically predisposed to cancer

If given the choice, at the age of 30, of knowing whether you are predisposed to develop cancer at the age of 55, 78% of people said they would prefer to know, reports a survey recently conducted by Roche UK. Four-fifths of the questioned group went on to state that, if found predisposed to developing cancer, they would then take preventative measures to reduce that risk, such as quitting smoking or drinking alcohol. The survey also enquired into people's attitudes to ageing. Although 30% of

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