LACTOFERRIN

A natural molecule may be leading the way as a new anticancer agent in humans

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Predictable treatment outcomes in Naturopathic Oncology are scarce when it comes to established disease. I.V. vitamin C, Hyperthermia, Mistletoe, Careseng, and Insulin potentiation therapy are just a few treatments often implemented by Naturopathic Doctors as ancillary treatment or as a last resort when all mainstream therapies fail. Despite the possible benefit of these agents, the challenge remains; which substances or combination of substances show evidence of positive outcome for patients with cancer? This article focuses on a natural molecule with the unique ability to prolong life in those with non small cell carcinoma lung cancer (NSCLC).

NSCLC - OUTCOMES OVER THE PAST 2 DECADES

NSCLC accounts for approximately 80% of all new lung cancer cases, with over a half million people in North America and Europe diagnosed each year (1).

Alarmingly, most patients diagnosed with NSCLC have late-stage disease or non-operative (Stage IIIB or IV). The current standard of care for these patients is systemic chemotherapy. Even with the available therapy, the five-year survival rate for these patients is less than 3% (1).

In the past 25 years, despite billions of dollars of research and a plethora of chemotherapeutic drugs, the outcome for advanced stages of lung cancer are still grim. Excision is the uncontested best treatment for early stages of lung cancer, however, this is not an option for lung cancer in advanced stages where there is lymph node involvement and bilateral infiltration. The textbook of Clinical Oncology "multidisciplinary approach" in 1983 states, "The five year survival of non-small cell carcinomas drops from 50% (stage I) to a mere 15% for stage II and to 1% for stage IV" (2). In 1995, the five-year survival rate of NSCLC was approximately 13% for Stage IIIA, 5% for Stage IIIB and 1% for stage IV (3). In 2007, the stats are virtually identical (3). Is mainstream medicine lost in cell biology and targeted molecular therapy for novel anti-cancer agents? Perhaps nature already contains molecules with diverse pleiotropic potential that should be the focus of cancer therapy.

For the time being, extending and improving quality of life in late stage cancer is the best that medicine has to offer. Recently, a natural biological molecule has come to the foreground of research for NSCLC.

LACTOFERRIN – A NATURAL MOLECULE PATENTED VIA RECOMBINANT TECHNOLOGY

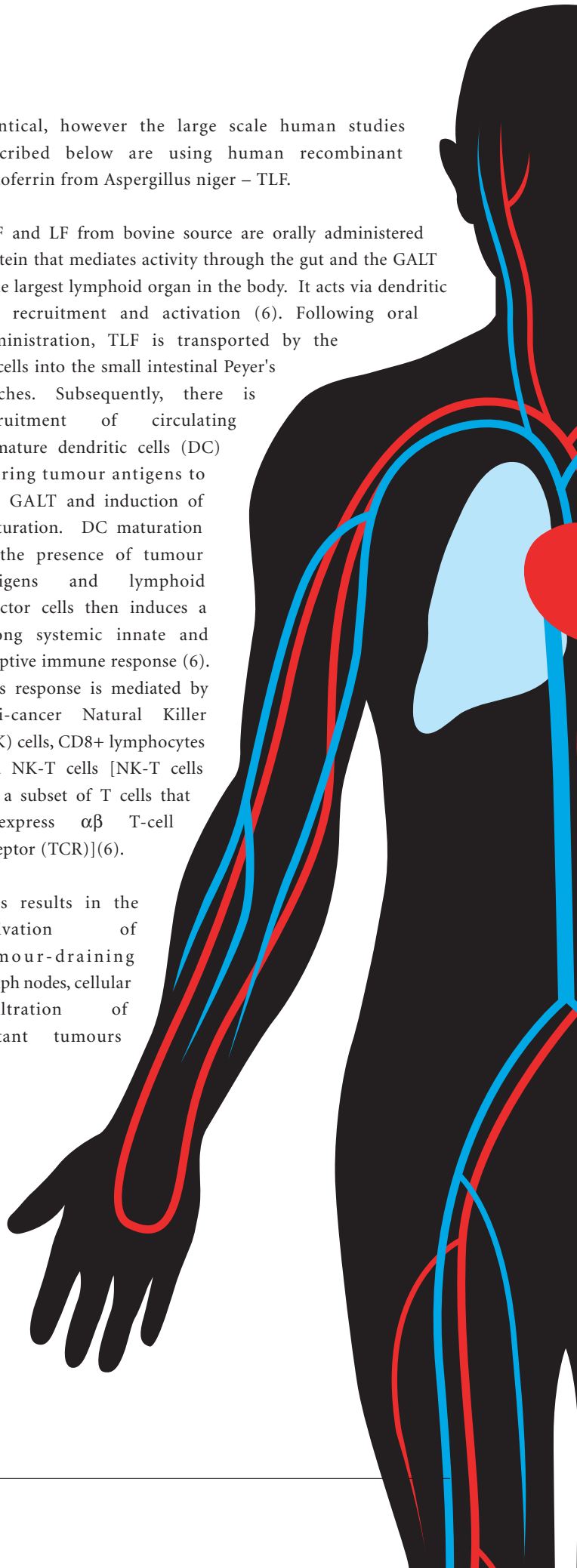
Lactoferrin (LF) is an iron-binding glycoprotein that was initially identified in breast milk as a protein of mammary epithelial cells. LF is known to scavenge free iron in fluids and inflamed areas, suppressing free radical-mediated damage and decreasing the availability of the metal (specifically Fe 3+) to invading microbial and neoplastic cells (4).

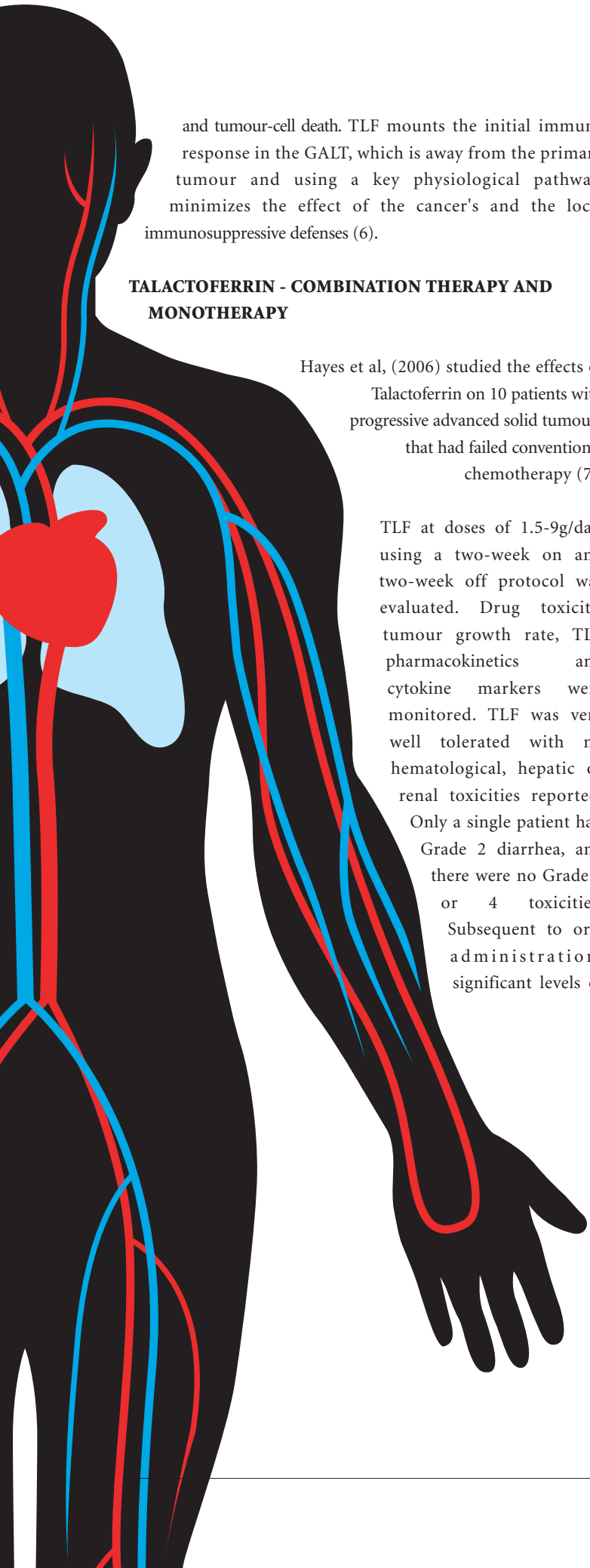
The immunomodulatory functions of bovine LF has been extensively studied in animal models (4). The mechanisms of action include activation of NK and lymphokine-activated killer cells, and enhancement of PMN and macrophage cytotoxicity (4). The immune-protective effects of LF against cancer cell development has been suggested to be mediated by interleukin-18, a cytokine with pleiotropic effects on immune cells (4). Interestingly, despite the preliminary bovine lactoferrin research, the recombinant human lactoferrin termed "Talactoferrin" (TLF) has been the focus of research in more large scale human trials.

Lactoferrin is broken down to many types of Lactoferrcin molecules. Research has suggested that the Lactoferrin B from bovine is more 'potent' than Lactoferrin from humans as an anti-microbial agent (5). The molecular structure of LF from bovine sources and LF from humans appear to be identical, however the large scale human studies described below are using human recombinant lactoferrin from Aspergillus niger – TLF.

TLF and LF from bovine source are orally administered protein that mediates activity through the gut and the GALT - the largest lymphoid organ in the body. It acts via dendritic cell recruitment and activation (6). Following oral administration, TLF is transported by the M-cells into the small intestinal Peyer's Patches. Subsequently, there is recruitment of circulating immature dendritic cells (DC) bearing tumour antigens to the GALT and induction of maturation. DC maturation in the presence of tumour antigens and lymphoid effector cells then induces a strong systemic innate and adaptive immune response (6). This response is mediated by anti-cancer Natural Killer (NK) cells, CD8+ lymphocytes and NK-T cells [NK-T cells are a subset of T cells that co-express αβ T-cell receptor (TCR)](6).

This results in the activation of tumour-draining lymph nodes, cellular infiltration of distant tumours





and tumour-cell death. TLF mounts the initial immune response in the GALT, which is away from the primary tumour and using a key physiological pathway, minimizes the effect of the cancer's and the local immunosuppressive defenses (6).

TALACTOFERRIN - COMBINATION THERAPY AND MONOTHERAPY

Hayes et al, (2006) studied the effects of Talactoferrin on 10 patients with progressive advanced solid tumours that had failed conventional chemotherapy (7).

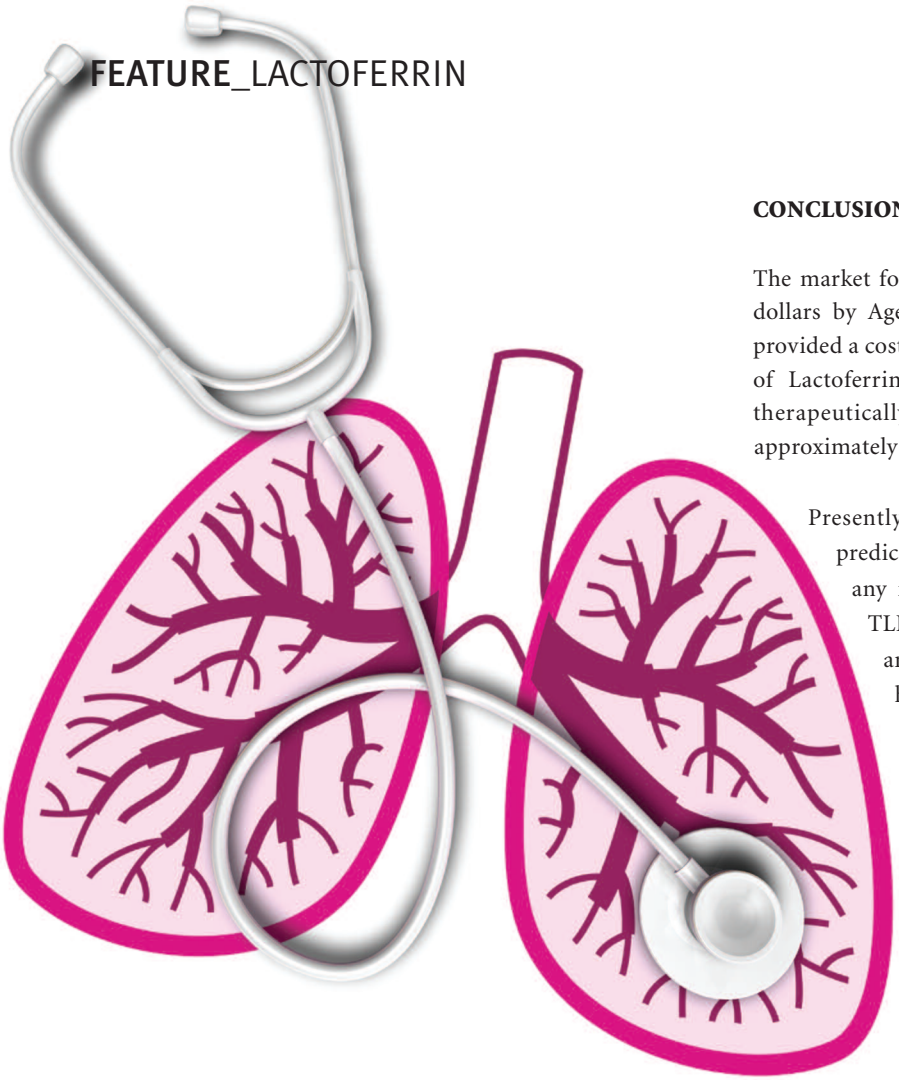
TLF at doses of 1.5-9g/day, using a two-week on and two-week off protocol was evaluated. Drug toxicity, tumour growth rate, TLF pharmacokinetics and cytokine markers were monitored. TLF was very well tolerated with no hematological, hepatic or renal toxicities reported. Only a single patient had Grade 2 diarrhea, and there were no Grade 3 or 4 toxicities. Subsequent to oral administration, significant levels of talactoferrin were undetectable in circulation, however a statistically significant increase in circulating IL-18; a known pharmacodynamic indicator of talactoferrin activity, was observed (7). Five of the eight patients who were radiologically evaluable had stable disease by Response Evaluation Criteria in Solid Tumours (RECIST) two months after starting treatment.

Seven of the eight patients (88%) had a decrease in tumour growth rate. The three patients in the study with non-small cell lung cancer (NSCLC) all survived for at least one year following the start of talactoferrin monotherapy. It should be noted that the individuals studied had stage IV NSCLC. The average lifespan of a person with diagnosed stage IV NSCLC is approximately 4.6 months (1,8). The authors concluded that, "Talactoferrin is a promising, well-tolerated new agent that should be evaluated further in patients with refractory metastatic cancer."

Agennix, a biotech company, studied Talactoferrin in 110 patients in a double-blind, randomized, placebo controlled, and multi-center Phase II clinical trial. Patients with advanced NSCLC (stage IIIb or IV) received standard first-line chemotherapy (carboplatin/paclitaxel; C/P) plus either TLF or placebo. The trial met its primary endpoint with a substantial improvement in response rate with TLF and chemotherapy. These results were presented at the 2005 meeting of the American Society of Clinical Oncology (ASCO) (8).

The addition of oral TLF to C/P improved the patients' response on all the tumour-related endpoints including response rate, progression-free survival (PFS), time to response and duration of response. Based on this information, combining TLF (if available) or bovine lactoferrin with Carboplatin/paclitaxel may be an important combination to improve the outcome of NSCLC.

In a previous Phase Ib human clinical trial by Agennix, patients with advanced or metastatic cancers who had failed standard chemotherapies received oral TLF single-agent therapy. The study included 36 patients with a range of tumour types. Responses (either partial or minor) were observed in patients with NSCLC. The median overall survival in the 12 NSCLC patients was 8.8 months, substantially better than the 4.6 months reported in second-line patients receiving Best Supportive Care (BSC). Supportive care included counselling, family support, pain relief and other symptomatic relief (8).



FDA FAST TRACK DRUG DESIGNATION – TALACTOFERRIN ALPHA

Agennix received Fast Track designation from the FDA for the clinical development of talactoferrin as a single-agent in patients with locally advanced or metastatic NSCLC, who have failed at least two prior systemic anti- cancer therapies. The Company had previously received fast track designation for first-line treatment of NSCLC in combination with chemotherapy.

One important question remains – is bovine Lactoferrin equivalent in clinical efficacy in NSCLC outcome? Some authors suggest that bovine lactoferrin is structurally and functionally equivalent to native human talactoferrin (6), while others suggest that Lactoferrin isolated from human intestinal brush-border have been shown to have a higher affinity for human intestinal epithelium (8). Considering that Agennix has the technology to synthesize 35,000 L of Lactoferrin using Aspergillus niger, they are able to capitalize on the effects of a natural molecule via mass production and educating thousands of oncologists

CONCLUSIONS

The market for Talactoferrin is projected to be 2.8-4.5 billion dollars by Agennix. Advanced Orthomolecular Research has provided a cost effective means through which effective dosages of Lactoferrin can be prescribed. Each "scoop" delivers a therapeutically appropriate dose of 4.6g, at a cost of approximately $200 per month.

Presently, Lactoferrin appears to have the most predictable human clinical efficacy as monotherapy of any natural agent (or drug) for late stage NSCLC. TLF is also approved for renal cell carcinoma use and treatment of diabetic ulcers with impressive human clinical data.

Very little progress has been made regarding the management of advanced NSCLC over the past 25 years. It is interesting to note that an orally administered natural medicine is leading the way for improved outcomes of this terminal disease. ■

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