

V. Clinical Sciences

D. Established and Evolving Immune-based Treatment Modalities

1. Glucocorticoids and immunosuppressants (also see Section III.A.)

LANDMARK ARTICLE:

Hench PS, Kendall EC, Slocumb CH, Polley HF.

Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions: A study in clinical physiology.

Arch Intern Med. 1950;85:546–666.

LANDMARK ARTICLE:

Boardley JE, Carey RA, Harvey AM.

Preliminary observations on the effect of adrenocorticotrophic hormone in allergic diseases.

Bull. Johns. Hopkins. Hosp. 1949; 85, 396–410.

The Nobel Prize for Medicine was awarded in 1950 to Hench for the discovery of synthesized ACTH and cortisol where it was efficaciously used in rheumatoid arthritis. This study was published around the time documenting efficacy in 5 asthmatic patients with eosinophilic sputums who improved and had resolution of sputum eosinophilia after a 3 week period of ACTH injections. It was later confirmed that oral cortisol had the same beneficial effects.

2. Nucleic acid based therapies (DNA vaccines, CpG, gene insertion, antisense nucleotides)

LANDMARK ARTICLE:

Tokunaga T, Yamamoto H, Shimada S, et al

Antitumor activity of deoxyribonucleic acid fraction from *Mycobacterium bovis* BCG. I.

Isolation, physicochemical characterization, and antitumor activity.

J Natl Cancer Inst. 1984 Apr;72(4):955-62.

A fraction extracted from *Mycobacterium bovis* strain BCG, which was composed of 70.0% DNA, 28.0% RNA, 1.3% protein, 0.20% glucose, and 0.1% lipid and of no detectable amounts of cell wall components such as alpha, epsilon-diaminopimelic acid and hexosamine, was found to possess strong antitumor activity. Repeated intralesional injection of this fraction, designated MY-1, without attachment to oil or a single intralesional injection of MY-1 emulsified in mineral oil caused the IMC carcinoma of CDF1 mice and line 10 tumor of strain 2 guinea pigs to regress and/or prevented metastasis very effectively. MY-1 after digestion with RNase, which contained 97.0% single-stranded DNA with a guanine-cytosine content of 69.8%, was more effective than undigested MY-1 against IMC and line 10 tumor, while MY-1 digested with DNase, which contained 97.0% RNA, had reduced activity, suggesting that the DNA from BCG possessed strong antitumor activity under certain conditions. Details of the extraction procedures and physicochemical characterization of MY-1 were also described.

LANDMARK:

Sato Y, Roman M, Tighe H, Lee D,

Immunostimulatory DNA sequences necessary for effective intradermal gene immunization.

Science. 1996 Jul 19;273(5273):352-4.

Vaccination with naked DNA elicits cellular and humoral immune responses that have a T helper cell type 1 bias. However, plasmid vectors expressing large amounts of gene product do not necessarily induce immune responses to the encoded antigens. Instead, the immunogenicity of plasmid DNA (pDNA) requires short immunostimulatory DNA sequences (ISS) that contain a CpG dinucleotide in a particular base context. Human monocytes transfected with pDNA or double-stranded oligonucleotides containing the ISS, but not those transfected with ISS-deficient pDNA or oligonucleotides, transcribed

large amounts of interferon-alpha, interferon-beta, and interleukin-12. Although ISS are necessary for gene vaccination, they down-regulate gene expression and thus may interfere with gene replacement therapy by inducing proinflammatory cytokines.

3. Cytokine receptors and receptor antagonists (IFN, antiTNF, etc)

LANDMARK PUBLICATION:

Strander H, Cantell K et al.

Clinical and laboratory investigations on man: systemic administration of potent interferon to man. *J Natl Cancer Inst* 1973 Sep; 51(3):733-42.

4. Probiotics

LANDMARK ARTICLE:

Majmaa H and Isolauri E.

Probiotics: A Novel Approach in the Management of Food Allergy.

J Allergy Clin Immunol. 1997 Feb; 99(2): 179-85.

BACKGROUND: The gastrointestinal microflora is an important constituent of the gut mucosal defense barrier. We have previously shown that a human intestinal floral strain, *Lactobacillus GG* (ATCC 53103), promotes local antigen-specific immune responses (particularly in the IgA class), prevents permeability defects, and confers controlled antigen absorption. **OBJECTIVE:** The aim of this study was to evaluate the clinical and immunologic effects of cow's milk elimination without (n = 14) and with (n = 13) the addition of *Lactobacillus GG* (5 x 10⁸) colony-forming units/gm formula) in an extensively hydrolyzed whey formula in infants with atopic eczema and cow's milk allergy. The second part of the study involved 10 breast-fed infants who had atopic eczema and cow's milk allergy. In this group *Lactobacillus GG* was given to nursing mothers. **METHODS:** The severity of atopic eczema was assessed by clinical scoring. The concentrations of fecal alpha 1- antitrypsin, tumor necrosis factor-alpha, and eosinophil cationic protein were determined as markers of intestinal inflammation before and after dietary intervention. **RESULTS:** The clinical score of atopic dermatitis improved significantly during the 1-month study period in infants treated with the extensively hydrolyzed whey formula fortified with *Lactobacillus GG*. The concentration of alpha 1-antitrypsin decreased significantly in this group (p = 0.03) but not in the group receiving the whey formula without *Lactobacillus GG* (p = 0.68). In parallel, the median (lower quartile to upper quartile) concentration of fecal tumor necrosis factor-alpha decreased significantly in this group, from 709 pg/gm (91 to 1131 pg/gm) to 34 pg/gm (19 to 103 pg/gm) (p = 0.003), but not in those receiving the extensively hydrolyzed whey formula only (p = 0.38). The concentration of fecal eosinophil cationic protein remained unaltered during therapy.

CONCLUSION: These results suggest that probiotic bacteria may promote endogenous barrier mechanisms in patients with atopic dermatitis and food allergy, and by alleviating intestinal inflammation, may act as a useful tool in the treatment of food allergy.