In 1978 Dr. Gideon Goldstein observed that the molecule levamisole, an effective antihelminthic agent as well as an immunoregulatory agent, exerted its putative immuno-regulatory action by mimicry of the thymic hormone thymopoietin.

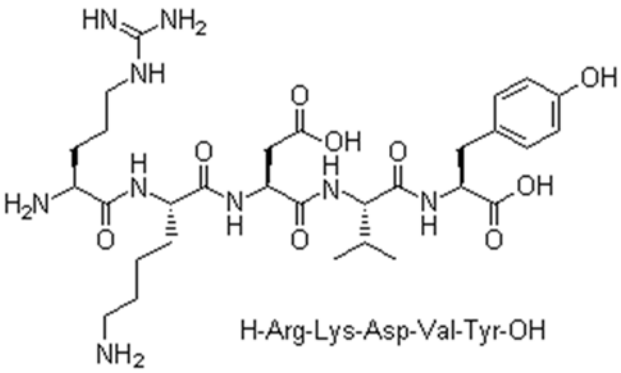
He suggested that levamisole formed a thymopoietin-mimetic tertiary structure and stimulated lymphocytes by its imidazole component or possibly metabolized to OMPI, a reducing compound which affects radical scavenging in activated lymphocytes.

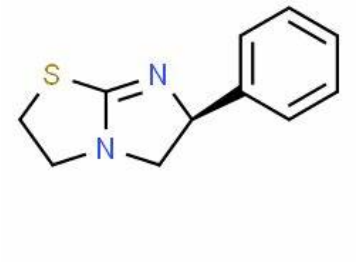
The body of work produced by Dr. Goldstein demonstrated the physiological effects of thymopoietin on the immune system including neutrophils, macrophages, and lymphocytes and most importantly on regulatory T cells that restore homeostasis in a dysregulated immune system.

Thymopoietin is a polypeptide hormone produced by the thymus and skin. An active region of thymopoietin is a pentapeptide, thymopentin, that has all the biological activities of the native hormone. The skin produces a regulatory molecule with one base modification in the structure that eliminates the neuromuscular action.

Thymopentin was developed into a therapy for chronic hepatitis B, chronic hepatitis C, an adjuvant therapy for chemotherapy-induced immune depression, immune insufficiency and immune suppression in patients with non-small cell lung carcinoma, malignant melanoma, hepatocellular carcinoma, breast cancer, non-Hodgkin's lymphoma, colorectal cancer, head and neck cancer, leukemia's, pancreatic carcinoma, and renal cell carcinoma.

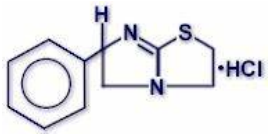
Biological experiments had determined that the thymus secreted a hormone that regulated neuromuscular transmission and the pentapeptide affected the neuromuscular regulatory function. The mechanism of action of thymopentin is not completely understood, but thymopoietin promotes T-cell differentiation and maturation, increases production of INF-γ, IL2, IL3, and expression of IL2 receptors following activation by mitogens or antigens, increase NK cell activity, and increases the production of migratory inhibitory factor, MIF.

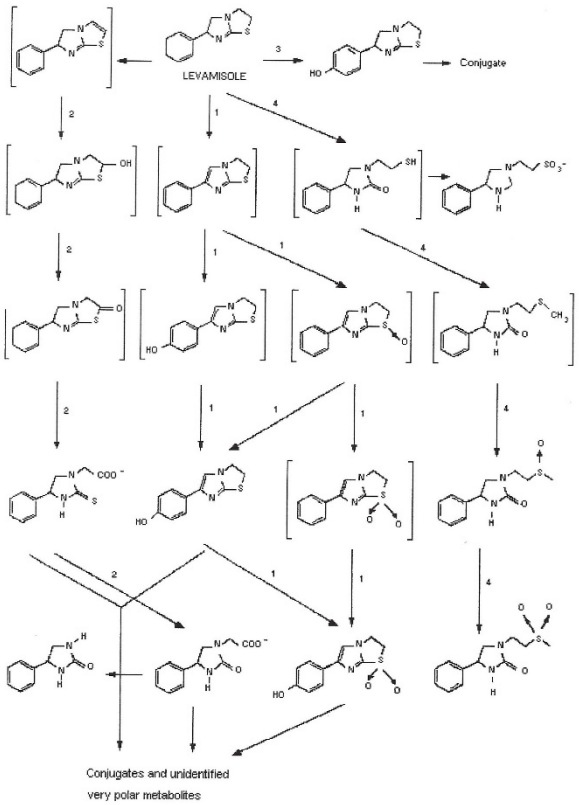




The similarity of the structure of thymopentin (above, left) and levamisole (above, right) are illustrated. The chemical levamisole phosphate is used in ruminants as an antihelminthic and levamisole HCl, a less toxic molecule (below, left), is use as an immunomodulatory agent in horses and people. Steroid-sensitive idiopathic nephrotic syndrome is a frequent disorder in children in which levamisole HCL was shown to be effective in maintaining a steroid-free remission. It is possible that there is an age-related difference in levamisole metabolism that needs investigation. The metabolites of levamisole is shown below, right.

There is an increased incidence of agranulocytosis associated with levamisole





in some adult patients, about 5% of the population. There may be an increased risk of agranulocytosis in patients carrying the leukocyte antigen B27 genotype.

One of NDRs interests is to identify the agranulocytic stimulating aspect of levamisole HCl, or a metabolite, allowing us to modify the chemical structure. Maintaining the pluripotent immunomodulating activities of a substituted levamisole HCl molecule, while preventing toxicity, may be a benefit to patients with neuromuscular degenerative diseases.