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## SUMMARY OF RESEARCH RELATING TO THE ANTI-INFLAMMATORY AND ANALGESIC PROPERTIES OF TOPICAL GALLIUM MALTOLATE

**Gallium maltolate** is a coordination complex consisting of gallium, a semi-metallic element, and maltol, a sugar-like compound found naturally in many foods. As an uncharged, pH-neutral molecule that is soluble in both water and lipids, gallium maltolate is non-irritating and well absorbed by the skin.<sup>3</sup>

### ANTI-INFLAMMATORY ACTIVITY OF GALLIUM

Numerous *in vitro* and animal studies have demonstrated that gallium can suppress pathological inflammation without being generally immunosuppressive. Gallium appears to be particularly effective at inhibiting abnormal T-cell mediated immunological reactions. Though it suppresses inflammatory T-cell activation and proliferation, gallium does not interfere with normal cytokine-activated killer T-cell activity or with the normal cytokine-mediated growth and repair of endothelial cells (which may actually be enhanced by gallium).<sup>9,11</sup> Gallium has also shown selective activity against pathological pro-inflammatory activity by macrophages.<sup>16,17,18</sup>

Intravenously administered gallium nitrate has shown efficacy in a number of rodent models of T-cell mediated autoimmune disease. Efficacy has been observed in adjuvant-induced arthritis, experimental autoimmune encephalomyelitis (a model for demyelinating diseases such as multiple sclerosis), experimental autoimmune uveitis, systemic lupus erythematosus, and Type 1 diabetes.<sup>1,10,15,22</sup>

Orally administered gallium maltolate demonstrated efficacy in two models of inflammatory arthritis in rats: adjuvant induced arthritis and streptococcus cell wall induced chronic arthritis.<sup>19</sup> In both models, oral gallium maltolate dose-dependently reduced joint inflammation, bone degradation, liver and spleen enlargement, and other measures of inflammation. No toxicity was observed.

Many of these immunomodulating effects are likely related to  $Ga^{3+}$  being a close chemical mimic of  $Fe^{3+}$ :  $Ga^{3+}$  competes with the transport and uptake of  $Fe^{3+}$ , but is biochemically non-functional because it lacks  $Fe^{3+}$ 's redox activity (its ability to exist in both divalent and trivalent states under physiological conditions).<sup>2</sup> Pro-inflammatory T-helper type 1 (Th-1) cells are much more sensitive to inactivation by iron deprivation (from, e.g., competition with gallium) than are anti-inflammatory, pro-antibody Th-2 cells.<sup>21</sup> The known antiproliferative activity of gallium (due to its interference with  $Fe^{3+}$ -dependent ribonucleotide reductase activity, and thus DNA synthesis), in this case on certain lymphocytes, may also contribute to gallium's immunomodulating activity.<sup>2</sup> Antiproliferative activity also makes gallium active against some cancers as well as some pathogenic bacteria and viruses,<sup>2,4,8</sup> further contributing to gallium's efficacy.

**Clinical observations** — Although no controlled human clinical trials have been performed, thousands of individuals have used topically administered gallium maltolate (0.5% in an emulsion of water and hydrophilic petrolatum) on a wide variety of skin lesions. Apparent efficacy has been observed in cases of psoriasis, acne vulgaris, acne rosacea, seborrheic dermatitis, eczema, hemorrhoids, herpes simplex lesions, and actinic keratosis.

### ANALGESIC ACTIVITY

Gallium maltolate has been administered topically to hundreds of individuals suffering from various types of pain. The first case was a 99-year-old woman who had severe facial (trigeminal) postherpetic neuralgia for four years and who had responded poorly or not at all to a large variety of systemic and locally administered narcotics, anesthetics, analgesics, anti-epileptics, anti-psychotics, and other medications. Topically applied, low-dose gallium maltolate provided nearly complete pain relief that lasted about six to eight hours.<sup>5</sup> Topically administered gallium maltolate has also been found effective in other individuals against postherpetic neuralgia

and against pain due to trigeminal neuralgia<sup>6</sup>, arthritis, tendinitis, insect bites and stings, spider bites, infections, burns, allergic reactions, plantar fasciitis, complex regional pain syndrome, cancer, and post-surgical facial pain<sup>12</sup>. The mechanisms for the analgesic activity are not known; they likely relate to gallium's anti-inflammatory activity, plus its possible interference with certain neuropeptides and matrix metalloproteinases (MMPs). Many neuropeptides, and all MMPs, are zinc-dependent, and gallium may act as a zinc mimic in some circumstances.<sup>2</sup> Several MMPs are implicated in the pathogenesis of neuropathic pain,<sup>7,11,13</sup> and substance P, a pain-associated neuropeptide, may be inhibited by high concentrations of zinc.<sup>20</sup> It is also possible that gallium is acting on the NMDA receptor or on one or more presently unknown pain pathways.

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