



# Site specific therapy: An integrative approach to treating melanoma

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**Summary** There have been many proposed theories for effectively treating melanoma, especially through the regulation of histamine. Histamine has been proven to be a major regulator of the immune system's T-helper cell subset balance and major shifts in this balance towards TH2 cytokines have contributed to diseases such as asthma, lupus and cancer. Histamine also causes suppression of interferon-induced proteins needed for anti-tumor response and activates T-suppressor cell function in cancers such as squamous cell carcinoma and melanoma. Scientific evidence has suggested the possibility of an antihistamine approach as treatment to these diseases and for melanoma, there has been great promise. This is due to the fact that melanotic cells have been elucidated to express histamine receptors and as a result, regulation of histamine could occur specifically at the site of these epidermal growths. Another factor to consider is how effective an inflammatory response can be when combined with regulation of histamine. Inflammation is a very powerful tool against pathogenic environments by causing cytokine recruitment and migration of dendritic cells to infected sites. Adequate stimulation of an inflammatory response at the specific site of any cancerous region would greatly weaken its evasive mechanisms. However, there are no reports showing high efficacy utilizing the benefits of regulating inflammation and histamine that could cause TH1 subset levels to predominate, down-regulate T-suppressor cells, up-regulate interferon-induced proteins and properly sustain migration of dendritic cells concurrently. These benefits have been proven in separate instances for a range of diseases but have not been assessed as a combined modality for melanoma therapy. Therefore successful melanoma treatment should integrate these principles involving: the use of H2 antagonists for preventing the negative effects of histamine, monoclonal antibodies to ensure an effective dendritic cell response, and routine pro-inflammatory induction at the specific site of the melanotic tissue to ensure recognition of the cancer that has evaded immunity.

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## Introduction

Histamine is formed by decarboxylation of amino acid histidine, and is a major component of mast cell granules present all throughout the body.

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When released histamine binds to one of the four receptors that have been identified-designated as H1, H2, H3, and fairly novel H4. Once histamine is bound, these receptors mediate different effects ranging from vasopermeability and dilation to functioning as presynaptic autoreceptors in the brain and heart. In the immune system, histamine is known to suppress cytotoxic T-lymphocytes, down-regulate some cytokines, and activate suppressor T-lymphocytes. The importance is how histamine tips the immune response to a TH2 subset specifically stimulating IL-4 and IL-10 production [4,5]. As a result TH1 subset cytokines such as IL-2, IL-12, and IFN- $\gamma$  become downregulated allowing epidermal growths to retain its pathogenicity and evasion of the immune system.

T suppressor cells also express histamine receptors causing a brake on immune response when activated by histamine [7]. So an effective treatment for melanoma would be to allow prolonged effects of TH1 cytokines, antagonizing T suppressor cells, and not suppressing inflammatory and anti-tumor responses. Also important is the need to stimulate Langerhan (dendritic) cells, found in the stratum spinosum of the epidermis, which can generate the permanent immunological memory required for remission. This can be done with the ensuing multifaceted approach.

## Proposed approach

First, appropriate testing such as RT-PCR should be done to check for the melanotic cells' mRNA expression of H2 receptors. This would indicate that H2 receptors were present and responsive to histamine exhibiting the ability to be blocked by Tagamet (cimetidine), an H2 antagonist.

Next, would be inducing a pro-inflammatory response at specific site of melanoma growth using radiation/nitrogen freezing for combined response of inflammation and up regulation of costimulatory molecules. This would cause peptides to be released from lysed tumor cells for antigen processing by dendritic cells and allow proper cytokine recruitment. Cytokines such as IL-1, IL-2, TNF- $\alpha$ , IFN- $\gamma$ , and GM-CSF can activate the proper T, NK, and Langerhans cells to destroy the cancer. However the problem is the need to sustain the levels of GM-CSF, TNF- $\alpha$ , IL-2, and IL-12 while suppressing IL-4, IL-10 and T suppressor cells.

This can be resolved with the administration of H2 antagonist (cimetidine), after initial inflammatory reaction either through the use of liposomes or transdermal administration. Scientific evidence

has proven that melanoma cells express considerable amounts of histamine and histamine receptors [1,2]. Using this knowledge along with the evidence of histamine shifting the balance toward a TH2 response [3,4], the antihistamine application would not only be effective in promoting TH1 cytokines but would also retard the effects of T-suppressor cell function. There is also another benefit of inhibiting histamine. There is a protein called interferon-induced protein (IP-10) that host anti-tumor response in melanotic cells mediated by induction of interferon- $\gamma$ . Histamine seems to inhibit or suppress this interferon mediated response leading to lower attack response against the tumor [8]. Using an H2 antagonist would resolve this issue as well.

Third, finalizing an effective migration of Langerhans cells to the cancerous region. IL-4 has been shown to inhibit the migration of human Langerhans cells through the downregulation of TNF receptor II expression that was induced by TNF- $\alpha$  and GM-CSF [5]. Besides the shift towards TH1 with antihistamines, an additional method would be specifically blocking IL-4 through the use anti-human IL-4 monoclonal antibody and anti-human IL-4 receptor monoclonal antibody [3]. This would ensure the proper processing of the cancerous antigens needed for complete T-cell activation of naïve, memory, and effector T cells [7].

## Conclusion

The majority of this treatment would provide very little risk or toxicity to the patient since there is a constant promotion to stimulate one's own defenses at natural levels within the specific site of the growth. No invasive methods are required and oral administration of antihistamine could be warranted for an enhanced effect. Due to these implications, appropriate testing for efficacy of this treatment can be done in vivo on melanoma patients as a clinical trial. Routine visits (i.e., bi-weekly) can be made to a health care professional who can meticulously check by use of caliper or other instruments for measuring the size of the lesion's regression. During these routine visits biopsies can also be taken from the cancerous area and tested for higher levels of TH1 cytokines (i.e., cytometric bead array, ELISA tests), for the absence of histamine (histamine assay), and/or tested for IP-10 production (ELISA) for a more detailed analysis. The integrative manner proposed would be adequate to ensure complete remission of any residual cancer cells because of the T and dendritic cells generating a permanent immunological memory response. As a result, this process can

contribute to the scientific awareness of the immune's orchestrated response whether it is epidermal or invasive. The knowledge of utilizing proper cytokines and regulating histamine and inflammatory levels during pathogenic or cancerous proliferations could be beneficial to many modalities of existing and novel treatment.

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