



IL-15 as a therapy for metastatic cancer and the IL-15 receptor as a target for immunotherapy of lymphoma and autoimmune diseases



**TEDCO/NIH/NCI Technology Showcase**

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*The Contrasting Roles of IL-2 and IL-15 in  
the Life and Death of Lymphocytes*

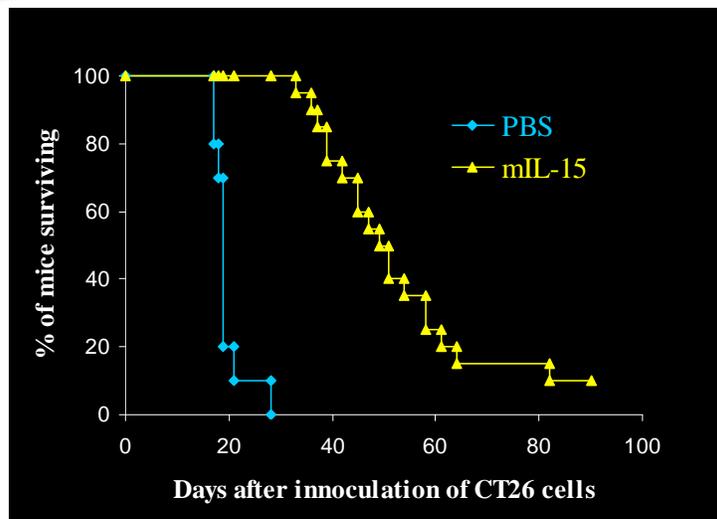


- 1. Both IL-2 and IL-15 stimulate the proliferation of T and B-cells and the generation and maintenance of NK cells.**
- 2. IL-2 is pivotally involved in AICD and the maintenance and fitness of CD4+CD25+ T regs, actions that prevent a T-cell immune response to self.**
- 3. IL-15 inhibits IL-2 mediated AICD and stimulates the development of NK cells and CD8+ memory phenotype T-cells that maintain an immune response to invading pathogens.**

*Opposing Effects of IL-2 and IL-15:  
Implications for Their Use in Cancer Therapy  
and as a Component of Vaccines*

- 1. IL-2** IL-2 has been approved for use in metastatic renal cell carcinoma; however in the presence of IL-2 the CTL generated may interpret the tumor cells as self and may die by AICD or may be inhibited by T-regs.
- 2. IL-15** With its activation of T-cells its inhibitory action on AICD and its facilitation of the persistence of memory CD8+ T-cells, IL-15 may be superior to IL-2 in the treatment of cancer and as a component of vaccines.

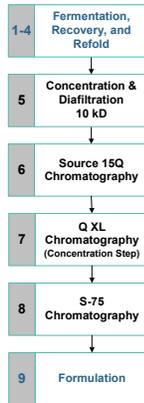
*IL-15 prolonged survival of mice bearing  
CT26 tumor*



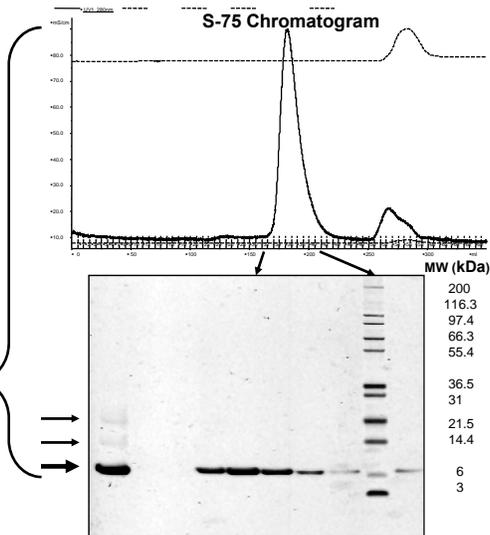
*Development of Recombinant Human Interleukin-15 into a cGMP Product Purification Development*



10 L Scale – 200 mg Yield



Step	Step Recovery	Overall Recovery
5	48%	48%
6	64%	30%
7	70%	22%
8	91%	20%
		<b>&gt; 95% pure</b>



*Technology Licensing Opportunity and Commercial Applications with IL-15*



**Areas where IL-15 Technology can be applied**

- The IL-15 cytokine codiscovered by Dr. Waldmann is being produced by the Biopharmaceutical Development Program (BDP) of the NCI for use in patients with metastatic malignant melanoma and renal cell cancer
- IL-15 will also be used in patients with HIV/AIDS receiving HAART Therapy
- IL-15 is being incorporated into molecular vaccines for cancer (Her2, HPV), HIV/AIDS, anthrax, malaria and tuberculosis

**Licensing Opportunity**

- Patent Application 10/538,974 Perera L, Oh S, Berzofsky J, and Waldmann TA. Recombinant Vaccinia Viruses Expressing IL-15 and Methods of Using the Same

*Regulatory Features are Required to Control IL-15 Expression*

- 1. IL-15 is an inflammatory cytokine that induces expression of TNF $\alpha$  and IL-1 $\beta$ .**
- 2. IL-15 inhibits self-tolerance mediated by AICD.**
- 3. IL-15 facilitates CD8 memory T-cell survival.**
- 4. If IL-15 were indiscriminately expressed it would lead to inflammatory autoimmune disease.**

*IL-2/IL-15R Beta as a Target for Immunotherapy*

- 1. The humanized antibody Hu-MiK-Beta-1 directed toward IL-2/IL-15R beta inhibits the transpresentation of IL-15 and thereby blocks the action of IL-15 on CD8 and NK-cells.**
- 2. Hu-MiK-Beta-1 was effective in prolonging cardiac allograft survival in cynomolgus monkeys.**
- 3. Trials of Hu-MiK-Beta-1 in rheumatoid arthritis, multiple sclerosis, TSP, refractory celiac disease and in LGL leukemia with granulocytopenia are planned.**

**Areas where anti IL-15 receptor directed therapy can be applied**

- An antibody to the IL-15 receptor beta subunit (IL-2/IL-15R beta) a receptor defined in the Waldmann Laboratory has been produced by the BDP of the NCI and is in phase I clinical trials in patients with CD8 leukemia/lymphoma and in those with a neurological disease caused by the retrovirus HTLV-I
- The antibodies to the IL-15 receptor will also be used for other diseases including celiac disease with CD8 lymphoma, Rheumatoid arthritis, and multiple sclerosis.

**Licensing Opportunity**

- Patent No. 5,833,983 Waldmann TA and Leonard W. Interleukin 2 receptor (IL-2Rbeta) and applications thereof

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