IL-15's arranged marriage

By Brian Moy, Staff Writer

Although **Novartis AG**'s recombinant IL-2, Proleukin aldesleukin, is one of the few FDA-approved drugs for metastatic melanoma and renal cell carcinoma, use of the drug is limited because of its severe side effects and limited activity. A group at the **National Cancer Institute** thinks pairing another interleukin, IL-15, with a CD40 agonist could result in better immune stimulation. The key will be making the combination sufficiently specific to avoid unwanted autoimmune side effects.

In a paper in *The Proceedings of the National Academy of Sciences*, the National Cancer Institute (NCI) group noted that IL-2 has a couple of key mechanistic drawbacks in cancer. First, the cytotoxic lymphocytes it generates "might recognize the tumor as self and undergo activation-induced cell death."¹

The other problem is that IL-2-dependent T_{regs} can dampen any immune response to tumors that the cytokine elicits.

IL-15, on the other hand, does the opposite. The cytokine activates cytotoxic T cells and NK cells and inhibits those cytotoxic lymphocytes from undergoing activation-induced cell death. IL-15 also plays a role in the persistence of CD8 memory T cells.

For any of these beneficial effects to occur, however, IL-15 needs to bind to IL-15 receptor- α (IL15RA) on the surface of dendritic cells (DCs) and monocytes.² The catch is that the receptor is only expressed at low levels on those cells.

As a result, treatment with IL-15 as a single agent probably would have limited therapeutic effects, said Thomas Waldmann, chief of the metabolism branch at NCI and corresponding author on the *PNAS* paper.

Enter CD40, a member of the tumor necrosis factor receptor superfamily that recently has been shown to increase expression of *IL15RA*,³ in addition to its known role in promoting T cell-mediated immunity and NK cell activation.

In mouse models of colon cancer, the NCI team showed that IL-15 plus an antibody that agonized CD40 significantly prolonged survival compared with that seen using either agent alone ($p < 0.001$).¹ NK cells isolated from mice receiving the combination displayed stronger cytotoxic activity against tumor cells than NK cells isolated from mice treated with either agent alone.

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—Rienk Offringa, Genentech Inc.

"Our immediate next steps are to show that IL-15 therapy is effective in treating cancer in humans," Waldmann told *SciBX*.

Combination of issues

The team hopes to have the combination in the clinic in about two years. But before starting clinical trials of the combination, the researchers plan to run a Phase I trial of IL-15 monotherapy to evaluate the safety and efficacy of the cytokine in patients with melanoma or renal cell carcinoma (RCC). That study is slated to begin this year.

Testing the combination could raise trial design issues, noted Rienk Offringa, a principal scientist at **Genentech Inc.**, a unit of **Roche**. "The present clinical feasibility of this particular regimen may be difficult, as neither IL-15 nor CD40 agonists are part of standard-of-care regimens for any tumor type," he said.

Nevertheless, said Offringa, both molecules "have been shown individually to have antitumor effects in preclinical models. It is not surprising that combining the two agents would have increased antitumor activity."

Dacetuzumab (SGN-40), a humanized mAb that targets CD40 from Genentech and **Seattle Genetics Inc.**, is in Phase II testing to treat relapsed or refractory diffuse large B

cell lymphoma (DLBCL) and is in Phase I testing to treat multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL).

Charles Prussak, managing director at **Memgen LLC**, said another concern is triggering a nonspecific immune response that could lead to autoimmune disease. "It is safer and more effective to introduce therapy directly into the tumor bed and stimulate an immune response only in the tumor, rather than nonspecifically activating the immune system throughout the body," he told *SciBX*.

Memgen's ISF35, a CD40 agonist, is in Phase II testing to treat chronic lymphocytic leukemia (CLL). The company plans to start a Phase II trial in NHL this year.

For blood cancers, Memgen said it can either directly inject ISF35 into the lymph nodes or remove the blood cells for treatment *ex vivo* and administer the modified cells systemically.

When treating solid cancers, according to the company, ISF35 would be injected directly into the tumor bed. The company plans to start a Phase I trial in metastatic melanoma this year.

Robert Coates, also a managing director at Memgen, said the company's CD40 ligand is better than mAbs at initiating an immune response. "We have found that using a membrane-bound CD40 ligand elicits a 10-fold greater immune response when compared to use with an antibody," he said.

Waldmann acknowledged that a ramped-up immune system carries a higher risk of autoimmune disorders. But he noted that metastatic malignant melanoma and metastatic RCC "have failed all standard therapy and justify a therapy with such a risk."

He said the findings reported in *PNAS* are neither patented nor licensed.

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COMPANIES AND INSTITUTIONS MENTIONED

Genentech Inc., South San Francisco, Calif.

Memgen LLC, Dallas, Texas

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Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland

Roche (SIX:ROG), Basel, Switzerland

Seattle Genetics Inc. (NASDAQ:SGEN), Bothell, Wash.