Interleukin-18: Powerful in a test tube, but a dud in the clinic

High-Dose Recombinant Interleukin 2 Therapy for Patients With Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993

Interleukin-18: Powerful in a test tube, but a dud in the clinic

A Phase 2, Randomized Study of SB-485232, rhIL-18, in Patients With Previously Untreated Metastatic Melanoma

Ahmad A. Tarhini, MD1, Michael Millward, MD2, Paul Mainwaring, MD3, Richard Kefford, MD4, Ted Logan, MD5, Anna Pavlick, MD6, Steven J. Kathman, MD7, Kevin H. Laubscher, MD8, Mohammed M. Dar, MD9, and John M. Kirkwood, MD1

“Among 63 subjects evaluable for response, [only] 1 achieved a partial response... Due to the low apparent level of clinical efficacy, the study was terminated at the end of stage 1.”

Tarhini et al., Cancer, 2009
IL-18 is restricted in tumors by an ultra high-affinity receptor decoy

**Robertson et al., Clinical Cancer Research, 2008**

**Zhou et al., Nature, 2020**
Decoy-Resistant IL-18 (DR-18)

**Diagram:**
- WT IL-18: IL-18BP binds to the receptor (IL-18Rα), activating TILs.
- DR-18: IL-18BP binds to the receptor (IL-18Rα), activating TILs.

**Graph:**
- Survival (%) over Days post engraftment.
- MC38 Tumor cells: 0.5×10^6.
- Tumor volume: 50-100mm^3.
- 0.32mg/kg IL-18/DR-18 (s.c.)

**Legend:**
- Saline (0/25)
- αPD1 (7/17)
- IL-18 (0/10)
- DR-18 (27/39)
- IL-18+αPD1 (4/10)
- DR-18+αPD1 (9/10)

**Article:**
**IL-18BP is a secreted immune checkpoint and barrier to IL-18 immunotherapy**

Zhou et al., Nature 2020
Translating DR-18 into the clinic:

Phase I trial of lead DR-18 variant ST-067 to begin in Summer 2021

Yale spinout re-engineers an immunotherapy GSK, others once abandoned

Simcha debuts with $25M to advance custom-built IL-18 for cancer

Engineering a better immunotherapy to outwit cancer — and launch a biotech