CD40L and other TNF SuperFamily ligands as vaccine adjuvants
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TNF SuperFamily

A treasure trove of biologicals

- 19 ligands, all trimers
- Blockers are the most valuable source of biological drugs
- 5 TNFSFs are in the NCI’s list of 20 most desirable immunotherapy agents
TNFSF activity requires ≥ 2 trimers
Receptor clustering is required for activation

no activation  strong activation
MultimericBio’s UltraLigands™

TNFSF fusion to a multimerizing scaffold

- TNFSF extracellular domain fused to multimerizing scaffold
- Surfactant protein D (SP-D) scaffold $\rightarrow$ 4 trimers, plus higher order multimers
- Acrp30 scaffold $\rightarrow$ 2 trimers
- Issued and pending patents in North America, Europe, and Asia

J. Virol. 80:1672, 2006
Lead molecule: CD40 Ligand (CD40L)

Key activator of dendritic cells (DCs)

Exogenous CD40L activates DCs

Endogenous CD40L on CD4+ T cells

Once formed, CD8+ killer T cells move to target
UltraCD40L™ DNA vaccine adjuvant

Augmenting CD8+ T cell responses

- 5-fold increase in CD8+ T cell response to a DNA vaccine for HIV Gag
- 5-fold increase using DNA prime/MVA boost format
- Augments antitumor vaccines

J. Virol. 80:1672, 2006
UltraCD40L™ in a cancer vaccine
CEA vaccination in CEA-transgenic mice

- Stringent neonatal tolerance model
- Only mice vaccinated with UltraCD40L™ survived CEA colon cancer challenge

Submitted.
Advanced adjuvant combinations

UltraCD40L™ + TLR + inflammasosome agonists

- Most difficult tumor immunotherapy model: established B16F10 melanoma
- Cure requires combining UltraCD40L™ with CpG/poly(I:C) and extracellular ATP (ATPe)
- First application of ATPe to tumor immunotherapy
- Patent pending in North America, Europe, and Asia

Submitted.
UltraCD40L™ grows B cell APCs
Generates CD8+ T cells for adoptive immunotherapy

- Unlimited amounts of APCs from small amounts of blood, unlike DC harvests using leukapheresis
- Antigens can be introduced by peptide pulsing or RNA transfection
- Used to grow anti-tumor or anti-viral CD8+ T cells for adoptive immunotherapy
- Can be injected systemically for anti-tumor effects
MultimericBio Pipeline

UltraLigand™ needed to use TNFSFs

- Chronic Hepatitis B Virus (HBV) therapeutic vaccine using UltraCD40L™ adjuvant – Phase I clinical trial planned
- Tumor immunotherapy using UltraCD40L™: lymphoma; melanoma; ovarian cancer; bladder cancer – preclinical
- Adoptive immunotherapy of cancer using CD40L-activated B cell APCs – preclinical
- Partnering for other vaccines