Fully Human Antibodies Against Programmed Cell Death Protein 1 (PD1)

Human anti-PD1 antibodies have been produced from immortalized isotype-switched B cells isolated from human ovarian cancers containing tertiary lymphoid structures (TLS). These B cells were then subjected in vitro to a proprietary affinity maturation process that created amino acid changes in the secreted antibody that resulted in novel fully human anti-PD1 antibodies. TLS are highly organized structures resembling lymph nodes where T and B cells co-localize, and 15-20% of ovarian cancers contain TLS that are associated with better prognosis. This is consistent with the function of anti-PD1 antibodies that work as checkpoint inhibitors, blocking a signal preventing activated T cells from attacking the cancer, thereby allowing the immune system to engage the cancer.

COMMERCIAL OPPORTUNITY

- Two anti-PD1 antibodies were among the top six Pharma Drugs by sales in 2018. Nivolumab marketed as Opdivo by BMS had $7.5B in sales in 2018 and Pembrolizumab marketed as Keytruda by Merck had $7.1B in sales in 2018. Both antibody therapies were initially approved in 2014. A third anti-PD1 antibody Cemiplimab marketed as Libtayo by Regeneron was approved in 2018.
- Pembrolizumab is used to treat inoperable or metastatic melanoma, metastatic non-small cell lung cancer, and is used for second-line treatment for head and neck squamous cell carcinoma, after platinum-based chemotherapy, and for the treatment of adult and pediatric patients with refractory Hodgkin's lymphoma. Other indications for Pembrolizumab include urothelial carcinoma, gastric cancer, cervical cancer, hepatocellular carcinoma, and renal cell carcinoma.
- In 2017 the FDA approved Pembrolizumab for any unresectable or metastatic solid tumor with biomarkers for mismatch repair deficiency or microsatellite instability. This was the first time the FDA approved a cancer drug based on tumor biomarker status rather than tissue histology, so that Pembrolizumab is called a tissue-agnostic drug.

TECHNOLOGY

A protocol was used to separate, activate and immortalize B cells from freshly dissociated advanced serous ovarian carcinomas from patients with TLS. Freshly resected stage III/IV ovarian carcinomas from naive patients are routinely obtained through an IRB approved protocol. Tissues are mechanically dissociated and cryopreserved. B cells can be purified from every dissociated ovarian carcinoma and can be immediately activated with CD40 agonists plus IL-21 and immortalized using EBV. OCT blocks can be generated for histological analysis and identification of TLS through IHC analysis, using CD19 and CD3 antibodies. Before cryopreservation, IgG can be purified from immortalized B cells with resins that selectively capture IgG of IgA (Thermo) and sent to CDI Laboratories for determination of their specificities using *HuProt* proteome arrays, which contain >80% of the human proteome. A proprietary in vitro protocol was used to induce affinity maturation in the B cells resulting in novel antibodies.

PUBLICATION/PATENT

- US provisional patent application filed March 29, 2019 for Dr. Jose Conejo-Garcia

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