Development of A Humanized Anti-IL-22 Antibody for Cancer and Inflammation Therapy

Jian Chen, Cathy Chang, Gerhard Frey, Haizhen Liu, Jing Wang, William J. Boyle and Jay M. Short

BioAtla, Inc. 11085 Torreyana Road, San Diego, CA 92121

Abstract No. 1405

INTRODUCTION

Interleukin-22 (IL-22) is an inflammatory cytokine implicated in autoimmune diseases such as psoriasis, atopic dermatitis, and ulcerative colitis (1). Additionally, IL-22 has been linked to promoting epithelial cell proliferation, stemness and tumorigenesis in cancer, often associated with a more aggressive phenotype across various cancers, including inflammatory colon cancer models (2).

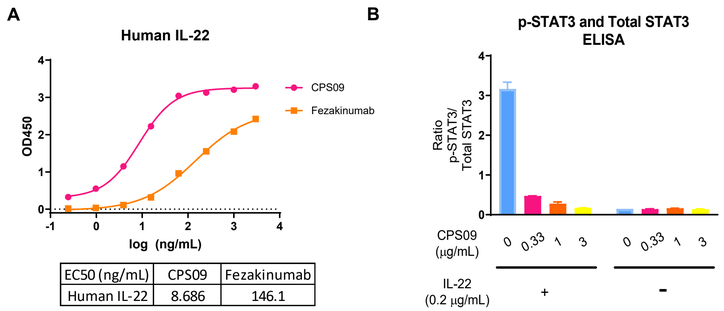
IL-22 plays a pivotal role in this pathogenic process by driving the activation of STAT3 and other signaling cascades. Recent studies have demonstrated that neutralizing IL-22 can reduced dysplasia and tumor development in preclinical models (3-5). However, despite these findings, the application of anti-IL-22 therapy for cancer and autoimmune diseases has not been clearly defined, likely due to challenges in identifying the appropriate disease indications and the relative low potency and efficacy of existing treatments. Thus, there remains an opportunity to explore the potential of more potent anti-IL-22 therapeutics.

BioAtla has developed humanized anti-IL-22 antibodies with high affinities to human, cynomolgus and mouse IL-22 using our proprietary antibody discovery and engineering platforms (6). In our previous report, we demonstrated that our anti-IL-22 antibody CPS09 inhibited IL-22-induced p-STAT3 activities. In addition, CPS09 showed a 10-fold increased binding activity to human IL-22 compared to Fezakinumab, previously developed by Pfizer for the treatment of autoimmune diseases.

Here, we developed an inflammation-driven sporadic colitis-associated colorectal (CAC) cancer mouse model and an imiquimod-induced psoriasiform skin inflammation mouse model to assess the efficacy of CPS09 *in vivo*.

RESULTS

1. CPS09 exhibits high affinity binding to human IL-22 and effectively inhibits IL-22-induced p-STAT3 activities



EC50 (ng/mL)	CPS09	Fezakinumab
Human IL-22	8.686	146.1

Figure 1. *In vitro* functional assays of CPS09. (A) Affinity ELISA binding assays of CPS09 and Fezakinumab. The plates were coated with 1 μg/mL recombinant human IL-22. Binding of the antibodies to human IL-22 was quantified with an anti-hu-IgG HRP conjugated antibody. (B) CPS09 inhibits human IL-22 induced STAT3 phosphorylation in a dose-dependent manner. CPS09 and human IL-22 were co-incubated for one hour. The HT29 cells were treated with indicated concentrations of CPS09 with/without IL-22 for one hour. Total and phosphorylated STAT3 were measured by ELISA assays (CST, #7300 and #7305).

RESULTS

2. Administration of CPS09, both short term (3 weeks) and long term (10 weeks), significantly reduced tumor progression in an AOM/DSS-induced colitis associated mouse colorectal cancer model

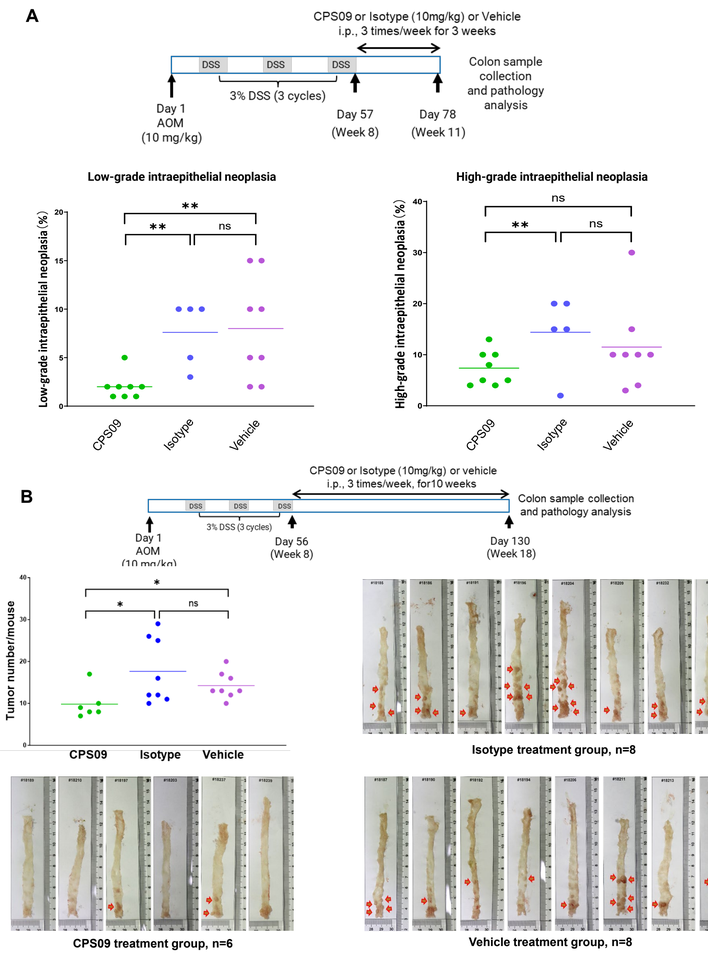


Figure 2. Evaluation of CPS09 in mouse CRC model. Female CD-1 mice were treated with 10 mg/kg of Azoxymethane (AOM) on day 1 followed by three cycles of 3% Dextran Sodium Sulfate (DSS). Subsequently, mice were treated with 10 mg/kg of CPS09, Isotype antibodies or vehicle as indicated during week 8 to week 11 (A) or during week 8 to week 18 (B). Colon samples were collected, and pathology analysis was performed. Low- and high-grade intraepithelial neoplasia were determined by histologic examination of tissue samples. Red arrows indicate larger tumors (>3mm diameter). P value: * <0.05, ** <0.01. ns: no significantly. Unpaired t-test was used for analysis.

3. CPS09 significantly reduced skin lesions in a skin inflammation mouse model

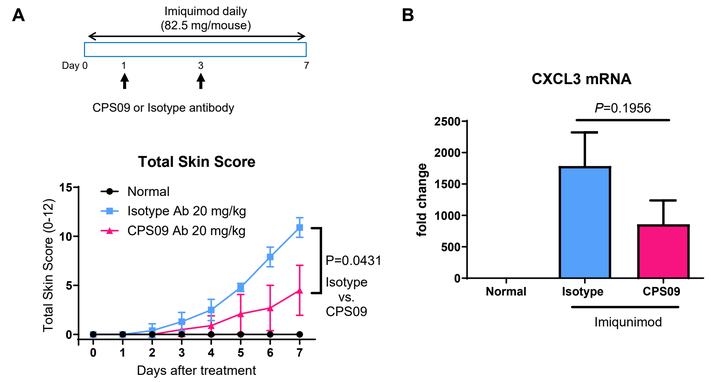


Figure 3. Evaluation of CSP09 efficacy in imiquimod induced psoriasis mice. (A) CPS09 prevented advanced manifestations of imiquimod induced skin inflammation. Imiquimod was applied daily to male BALB/c mice for 7 days. The mice received a single intravenous injection of 20mg/kg of CPS09 or Isotype antibody on day 0 and day 3. Erythema, scales, and skin thickness was assessed daily. Statistical analysis was performed using paired t-test. (B) Q-PCR analysis was performed for CXCL3 mRNA expression. RNA was isolated from mouse back skin. Statistical analysis was performed using unpaired t-test.

CONCLUSIONS

- The development of a potent, species cross-reactive anti-IL-22 antibody using BioAtla's antibody discovery and engineering platforms addresses previous challenges encountered in anti-IL-22 therapeutics. This breakthrough enables translational studies in relevant animal efficacy and safety models.
- CPS09 has demonstrated significant efficacy in reducing inflammation and tumor development in mouse models, thereby potentially overcoming the obstacles associated with anti-IL-22 therapeutics.
- BioAtla's Conditionally Active Biologics (CAB) technology has been leveraged to create a next-generation CAB-anti-IL-22 antibody, building upon the success of CPS09 research. This advancement enhances the safety margin and therapeutic index, particularly in targeting the inflammatory tumor microenvironment in colorectal cancer.

References:
1. Keir M.E., et al., J. Exp. Med. 2020, Vol. 217 No. 3.
2. Jiang R., et al., BMC Cancer 2013, 13:59.
3. Huber S., et al. ,Nature 2012, vol 491, p259–263.
4. McCuaig S., et al. , Clin Cancer Res 2020, 26:4313–25.
5. Kirchberger S., et al., JEM 2013, Vol. 210, No. 5.
6. Wheeler, C., et al., Abstract 6335, Cancer Res (2023) 83.