Novel mRNA-Encoded HPV Vaccine ABO2101 with APC Maturation Signal and Endolysosomal Trafficking Domain Demonstrates Superior T Cell-Mediated Immunogenicity and Efficacious Tumor Clearance In Vivo

4103

Liang Du, Jingshu Ma, Zhenxing Yang, Jinjuan Mao, Jijun Yuan, Wenjie Song, Bo Ying
Abogen Bioscience

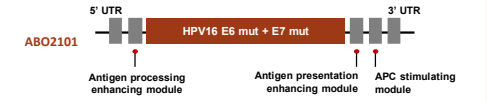
Abstract

Human Papillomavirus (HPV), particularly HPV16, is a known causative agent in anogenital and oropharyngeal cancers. Demand for safer and more efficacious therapeutics is pressing.

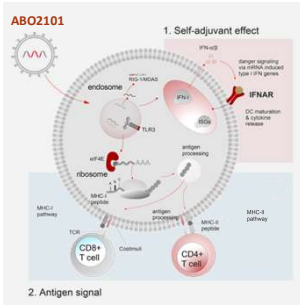
Our team developed ABO2101, an innovative mRNA therapeutic cancer vaccine for HPV16-associated cancers. ABO2101 features a unique antigen-expressing cassette enhancing antigen processing, antigen presentation and APC maturation. In murine and human-derived models, ABO2101 demonstrated superior T cell responses against HPV16 antigens compared to other vaccines. ABO2101 eradicated early and advanced tumors in mice, accompanied by increased HPV16-specific CD8+ T cells in the tumor microenvironment. In tumor prevention model, ABO2101 prevented tumor growth at various dosages, showcasing robust preventative capabilities. Combined with immune checkpoint inhibitors, ABO2101 showed a synergistic effect, suggesting potential for combinational clinical therapy.

ABO2101 represents a groundbreaking advancement in HPV-associated cancer treatment, supported by compelling preclinical data.

Science-driven designing of ABO2101 mRNA vaccine



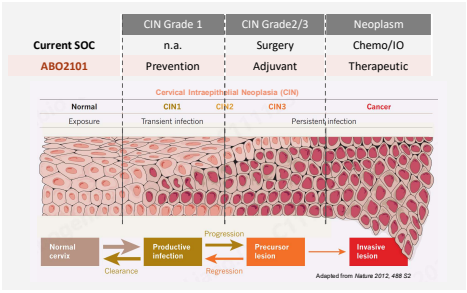
Abogen's antigen-expressing cassette is designed to amplify the fundamental working mechanism of antigen-presenting cells (APC). We have optimized modules to facilitate each step of antigen processing, antigen presentation by the major histocompatibility complex (MHC), and the activation of APCs. This optimization is coupled with a maximal expression capability achieved through UTR and mRNA codon design.



Recognition of mRNA by Toll-like receptors on immune cells, triggers a cascade of signaling events leading to the activation of type I interferon (IFN) genes. IFNs contribute to the activation of various components of the immune system, including DCs, natural killer cells and macrophages. The self-adjuvant effect of mRNA promotes the maturation of dendritic cells, enhancing their ability to present antigens to T cells via MHC-I and MHC-II pathways effectively. This maturation process is essential for the initiation of a potent adaptive immune response.

Overview of ABO2101 for HPV16+ cervical intraepithelial neoplasia and cervical neoplasm

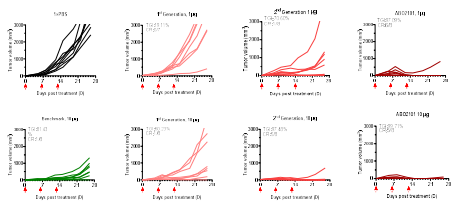
ABO2101 possesses the potential for broad application throughout the entire spectrum of HPV16+ cervical malignancies. It represents a safe preventive option for administration in patients with cervical intraepithelial neoplasia (CIN) Grade 1 to prevent disease progression. Furthermore, its high efficacy may reduce the necessity for invasive surgery in cases of CIN Grade 2/3. The current standard of care for cervical neoplasms includes chemotherapy in conjunction with immune checkpoint inhibitors. Supported by compelling preclinical evidence, ABO2101 exhibits the capability to eliminate both early-stage and advanced tumors as mono therapy or in combination with immune checkpoint inhibitors.



Optimization of antigen-expressing cassette enhanced the anti-tumor activity of ABO2101

Antigen-expressing cassette component	Abogen's 1st Generation HPV16+ vaccine	Abogen's 2nd Generation HPV16+ vaccine	Abogen's 3rd Generation ABO2101
Antigen processing module	+	+	+
Antigen presentation module		+	+
APC stimulating module			+

ABO2101 in HPV16+ tumor treatment

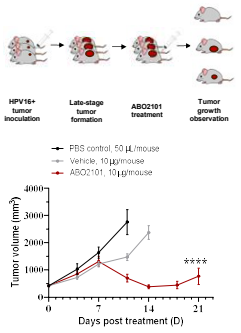


Different modules for antigen processing, antigen presentation, and APC stimulation, along with combinations thereof, were systematically evaluated alongside UTR sequence optimization to attain an optimal anti-tumor-specific immune response.

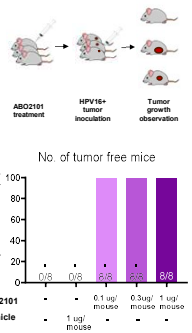
* An alternate sequence was selected distinct from its first-generation counterpart.

ABO2101 demonstrated excellent efficacy in both preventive and advanced tumor treatment model

ABO2101 in late-stage tumor treatment



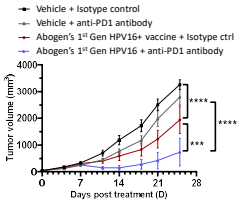
ABO2101 in tumor prevention



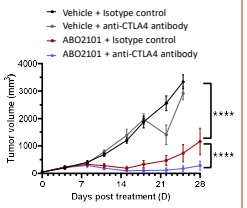
The potent anti-tumor efficacy of ABO2101 was demonstrated in HPV16+ advanced tumor model as a monotherapy. In HPV16+ positive tumor prophylactic model, a dosage equivalent to 1/100th of that required in advanced tumor models achieved complete tumor prevention. ABO2101 is poised to effectively prevent tumor incidence in CIN populations.

The synergistic effect of ABO2101 in combination with immune checkpoint inhibitors in tumor treatment

Abogen's 1st Gen HPV16+ vaccine + anti-PD-1 antibody in HPV16+ tumor treatment



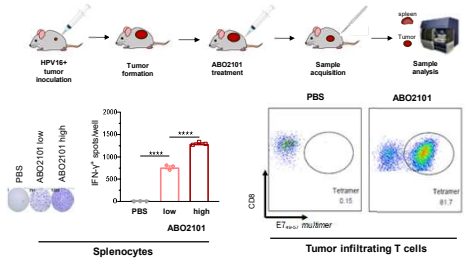
ABO2101 + anti-CTLA-4 antibody in HPV16+ tumor treatment



The combination of ABO2101/Abogen's 1st generation HPV16+ vaccine with immune checkpoint inhibitors, including anti-PD1 and anti-CTLA4 antibodies, displayed a synergistic effect in both immune-oncology sensitive and resistant animal models, suggesting a potential for combinational clinical therapy.

The combinations of ABO2101 with multiple other immune-oncology drugs were also evaluated in HPV16+ tumor models. Synergistic anti-tumor effects were observed in all tested scenarios, indicating the potential of ABO2101 for combination with immune-oncology drugs in clinical settings.

Specific T cell response was induced by ABO2101 in spleen and tumor microenvironment



ABO2101 effectively elicits specific T-cell activation and prominently expands tumor-specific T-cells within the tumor microenvironment. In accordance with its underlying mechanisms, ABO2101 exerts its anti-tumor effect through T-cell immunity.

Preliminary toxicity study of ABO2101 in NHP

- ABO2101 was administered intramuscularly at dose 0.3mg, 1mg and 3 mg per Cynomolgus monkey, once per week for 5 times;
- No signs of systemic toxicity at any dose levels;
- No adverse gross/organ weights/histopathology;
- MTD has not been identified, and the overall safety profile is favorable.

Summary

- Significant unmet medical needs exist for HPV-associated cancers, underscoring substantial market demand.
- ABO2101 is mRNA therapeutic cancer vaccine for HPV16-associated cancers. As a best-in-class candidate demonstrated by superior anti-tumor efficacy, ABO2101 holds promising prospects for clinical success.
- ABO2101 demonstrated a favorable safety profile in non-human primate studies.
- Currently, ABO2101 is undergoing IND-enabling development.
- An Investigator-Initiated Trial (IIT) is planned to promptly assess the clinical safety and potency of ABO2101.

Contact

Dr. Jijun, Yuan
President of Pre-Clinical Research
Abogen Bioscience
Email: jijun.yuan@abogenbio.com
Website: https://www.abogenbio.com/en

References

1. Human papilloma virus: A review study of epidemiology, carcinogenesis, diagnostic methods, and treatment of all HPV-related cancers, Med J Islam Repub Iran. 2021; 35: 65
2. Worldwide burden of cancer attributable to HPV by site, country and HPV type, Int J Cancer 2017, 141(4):664-670
3. Gaps and Opportunities to Improve Prevention of Human Papillomavirus-Related Cancers, J Womens Health 2021, 30(12): 1667–1672
4. HPV16 E6-specific T cell response and HLA-A alleles are related to the prognosis of patients with cervical cancer, Infect Agents Cancer 2021, 16:61
5. Combining Immune Checkpoint Blockade and Tumor-Specific Vaccine for Patients With Incurable Human Papillomavirus 16–Related Cancer A Phase 2 Clinical Trial, JAMA Oncology 2019, Volume 5 Number 1
6. Profiling HPV-16–specific T cell responses reveals broad antigen reactivities in oropharyngeal cancer patients, J. Exp. Med. 2020, Vol. 217 No. 10
7. Dual PD-L1 and TGF-b blockade in patients with recurrent respiratory papillomatosis, J Immunother Cancer 2021, 9(8): e003113