Innovative mRNA-based CD19/CD3 T Cell Engagers for the Treatment of B Cell Hematological Malignancies

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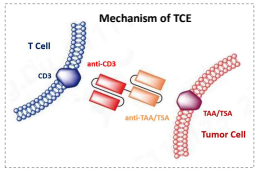
Abstract

T Cell Engager (TCE) immunotherapies have revolutionized cancer treatment. Blinatumomab, a bispecific CD19/CD3 TCE, provides effective treatment against relapsed or refractory B-cell Acute Lymphoblastic Leukaemia (B-ALL). Challenges arise due to Blinatumomab protein's short half-life, demanding continuous infusion over 28 days per cycle and its association with cytokine release syndrome (CRS).

To address these issues, mRNA technology was leveraged to develop CD19/CD3 TCE-encoded mRNAs, with enhanced in vivo protein exposure through sustained in-situ production of protein from mRNA, and altering transient pharmacokinetic (PK) profile to mitigate CRS risk. Comparative studies validated that mRNA-produced TCEs are similar to recombinant proteins in structure and function. PK studies in mice and primates demonstrated over 10-fold increased TCE exposure post dose of TEC-encoded mRNA compared to protein counterparts, resulting in superior antitumor efficacy in ALL and lymphoma models. mRNA-treated animals exhibited reduced IL6 cytokine induction, indicating lower CRS risk. Promising results prompted an investigator initiated trial with mRNA encoding CD19/CD3 TCE in relapsed and/or refractory ALL patients, showing acceptable safety profiles and good alignment with predicted pharmacokinetic profile. These findings underscore the potential of mRNA-encoded CD19/CD3 TCEs in clinical settings, indicating the broad prospect of leveraging mRNA modalities to transform TCE proteins.

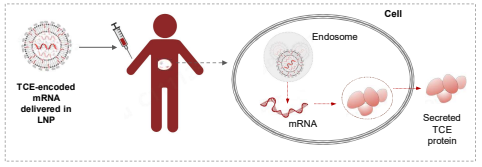
mRNA encoding T cell engager as a therapeutic agent



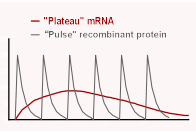
T Cell Engager (TCE) activates T cell and kills tumor by simultaneously binding the T cell surface antigen and the tumor cell surface antigen.

Blinatumomab, the first FDA approved TCE, targets CD19 on malignant B cells. Long-term overall survival and improved MRD-negative response rates in Blinatumomab treated patients evidences the success of this drug. Nevertheless, poor patient compliance and cytokine release syndrome are the two major issues with the blinatumomab therapy.

The therapeutic TCE protein-encoding mRNA is safeguarded by Abogen's patented lipid nanoparticle formulation and administered to patients via intravenous injection. Upon entering the human body, the mRNA-LNP complex is internalized by targeted organ cells. Within these cells, the mRNA is released from the endosome and undergoes translation, giving rise to the therapeutic TCE protein. The soluble TCE protein is secreted from the cells and execute its anti-tumor function.



The rationale & optimization strategies for mRNA encoding CD19/CD3 T cell engager



Gradual and sustained release of TCE protein by mRNA delivers an optimal therapeutic window

mRNA encoding protein

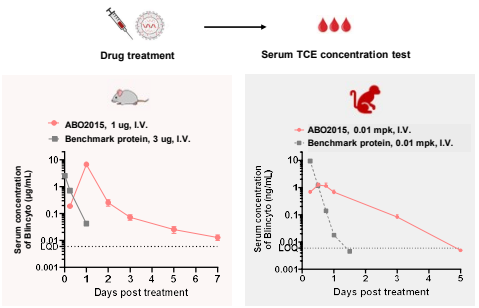
- Increasement of functional protein's exposure
- Higher patient compliance with lowered dosing frequency
- Less toxicity with gradual expression of drug protein
- Improved therapeutic window

Description of drug molecules appearing in this poster

Drug ID	Modality	Features	Improvements
Benchmark	Protein	• Blinatumomab	• NA
ABO2015	mRNA-LNP	• mRNA encoding Blinatumomab protein sequence	• PK profile was improved • CRS toxicity was reduced
ABO2203	mRNA-LNP	• mRNA encoding an novel CD19/CD3 bispecific • The anti-CD3 arm was optimized to reduce CRS associated toxicity • Protein structure was engineered to extend its half-life	• Expression-ability of mRNA was optimized • PK profile was further improved • CRS toxicity was further reduced

ABO2015 encodes the amino acid sequence of Blinatumomab, with subsequent experiments poised to elucidate comparative attributes between it and the recombinant Blinatumomab. These experiment anticipates shedding light on the distinctive characteristics inherent to the modality of mRNA encoding therapeutic proteins.

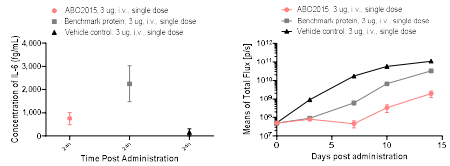
Favorable pharmacokinetic profile attained with in situ therapeutic protein production by mRNA encoding TCE



Favorable pharmacokinetic profile was demonstrated in both ABO2015 administrated mice and monkey compared with the protein counterpart. Sustained release of TCE protein in situ by mRNA greatly increased therapeutic protein exposure while the gradual release may facilitate the natural priming of T cells.

Less IL-6 release together with better anti-tumor efficacy was demonstrated in ABO2015 treated animals

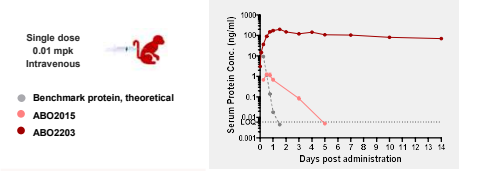
Less IL-6 cytokine release together with better anti-tumor efficacy was demonstrated in ABO2015 treated animals



Animals treated with ABO2015 exhibited superior antitumor efficacy compared to those treated with the protein counterpart. Furthermore, IL6 cytokine levels induced in the ABO2015 group were significantly lower than those in animals treated with the protein, suggesting a diminished risk of cytokine release syndrome (CRS) induction. This optimized therapeutic window associated with mRNA modality stems from the gradual and sustained release of TCE protein in situ by translation of mRNA, facilitating natural priming of T cells and enhanced drug exposure for improved anti-tumor efficacy.

Pharmacokinetic profile of ABO2203, mRNA encoding a novel half-life extended CD19/CD3, in NHP

In further pursuit of reduced dosing frequency and mitigated risk of CRS induction, we focused on optimizing the anti-CD3 arm and protein structure, resulting in the development of a novel half-life extended CD19/CD3 bispecific. The new protein sequence is encoded by mRNA, encapsulated within Abogen's proprietary lipid nanoparticle formulation. We designate this mRNA encoding CD19/CD3 T cell engager as ABO2203.



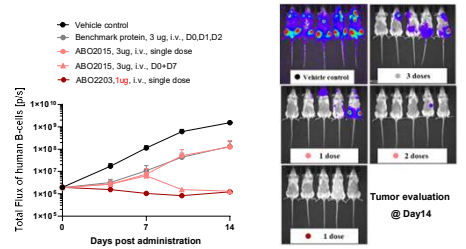
ABO2203, 0.01 mpk, I.V.

$t_{1/2}$	day	18.8
T_{max}	day	1.50
C_{max}	ng/mL	202
MRT_{inf}	day	28.2
AUC_{last}	day*ng/mL	1462
AUC_{inf}	day*ng/mL	3373
AUC Extrapolated	%	50.9

The presented data illustrates the PK profile of ABO2203 following a single injection (dosage: 0.01 mg/kg) in non-human primates. In comparison to ABO2015, an mRNA encoding the Blinatumomab sequence, ABO2203 exhibits a substantially prolonged half-life of 18.8 days. Moreover, the expression capability of ABO2203 is markedly enhanced, evidenced by a Cmax of 202 ng/mL at the dosage of 0.01 mg/kg.

Enhanced antitumor efficacy of ABO2203 demonstrated with reduced dosage and dosing frequency

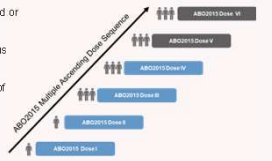
In a human B-cell acute lymphoblastic leukemia (ALL) model, evaluation was conducted to test if the advantageous pharmacokinetic profile of ABO2203 could confer superior anti-tumor efficacy. Compared with the administration of multiple doses of the benchmark protein, ABO2203 significantly outperformed by completely eradicating tumors at a third of the dosage with a single administration.



Investigator initiated study of ABO2015 demostrates acceptable safety and predicted PK profile

ABO2015 is currently in investigator initiated trial in r/r ALL patients

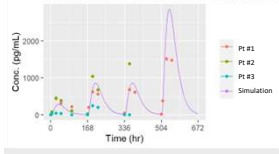
- **Subjects:** adult patients with relapsed or refractory precursor B-cell ALL
- **Route of administration:** intravenous
- **Goals:** to evaluate the safety and tolerability and to determine the RD of ABO2015



Safety

- The first 4 cohorts have been completed with acceptable safety profile;
- All observed non-hematological AEs are G1/G2.

Simulated and observed CD19/CD3 protein concentration in patient's serum



Pharmacokinetic profile

As depicted in the left graph, the expressions of CD19/CD3 bispecific antibodies in patients' peripheral blood is in good agreement with the predictions derived from preclinical data.

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