KPL-404, a CD40 antagonist, blocked antigen-specific antibody responses in an *in vivo* NHP model and demonstrated strong PK/PD correlation

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BACKGROUND

Role of CD40-CD40L pathway in adaptive immune cell responses

- Antigen recognition by T-cells in the context of TCR-MHC II results in upregulation of CD40L by T-cells and increased CD40L-CD40 interaction with Antigen Presenting Cells (APCs), which leads to activation of T-cells and APCs and secretion of cytokines.
- In the context of T-cell-dependent antigens, antigen-primed B-cells require CD40-CD40L interaction provided by activated T-cells to produce antibodies and form germinal centers (GC) where B-cells proliferate, differentiate, and undergo isotype class switch and affinity maturation (**Figure 1**)

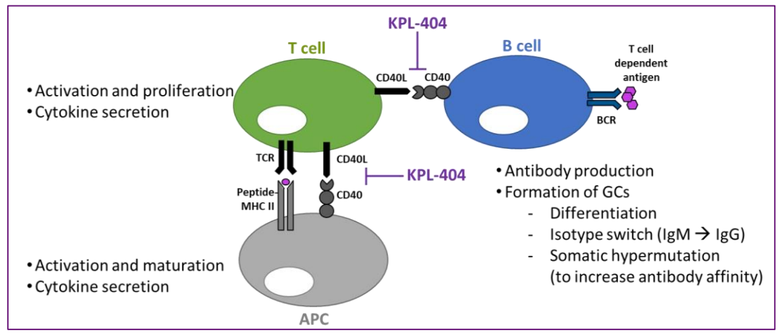
Therapeutic Hypothesis for KPL-404 in Autoimmune Diseases

- KPL-404, a humanized monoclonal IgG4 that targets CD40 and blocks CD40-CD40L interaction, is a potential therapeutic option for autoimmune diseases
- Dysregulation of the CD40-CD40L pathway has been implicated in multiple autoimmune disease pathologies such as Systemic Lupus Erythematosus, Rheumatoid Arthritis, Sjogren's Syndrome and Graves Disease

Objectives

- To determine KPL-404 pharmacokinetics and assess KPL-404 efficacy in engaging CD40 target and blocking antigen-specific primary and secondary antibody responses

Figure 1: Role of CD40-CD40L Pathway in Adaptive Immune Cell Responses



METHODS

Study Design

- KPL-404 was tested in an antigen priming/re-challenge model using T-cell-dependent antigens Keyhole limpet hemocyanin (KLH) and tetanus toxoid (TT) in cynomolgus monkeys (n=7 animals/group) over 56 days (**Figure 2**)

Groups 1-4:

- KPL-404 1, 5, or 10 mg/kg IV vs. control (0 mg/kg) administered on d0 and d28
- KLH+TT IM priming dose was given on d0 (0, 1, 5, and 10 mg/kg groups), with re-challenge on d28 (0, 1, and 5 mg/kg groups)

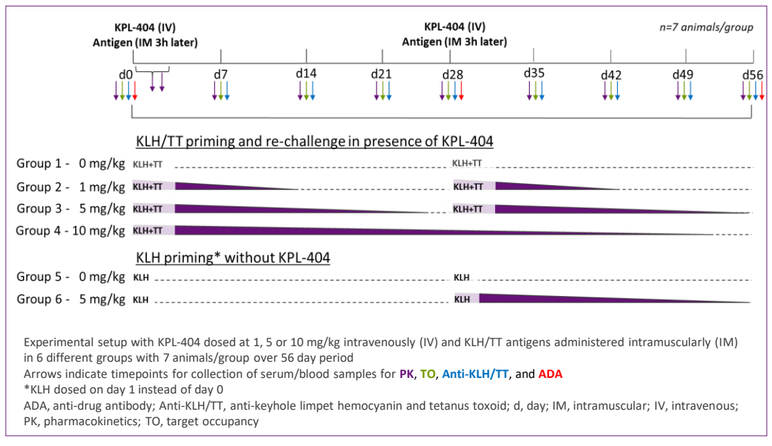
Groups 5-6:

- Animals primed with KLH IM (without KPL-404) on d1 and re-challenged with KLH IM following KPL-404 (5 mg/kg IV) administration on d28

Endpoints assessed

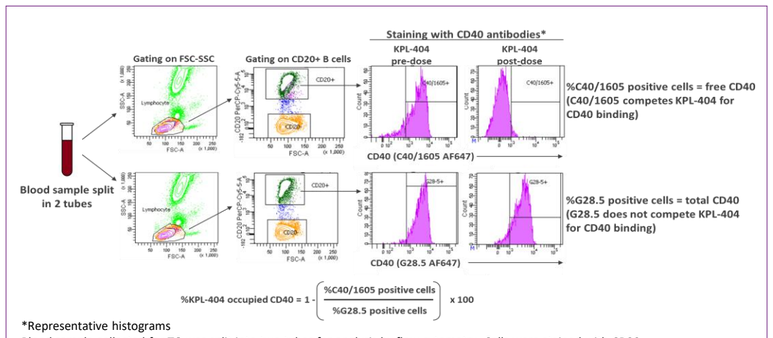
- KPL-404 serum pharmacokinetics (PK), anti-drug antibodies (ADA) to KPL-404 and KPL-404-mediated pharmacodynamics (PD)
  - anti-KLH/TT serum IgM and IgG responses (ELISA); CXCL13 (marker for GC activity) in serum (ELISA); CD40 target occupancy (TO) in blood (flow cytometry) (**Figure 3**)

Figure 2: Study Design



Experimental setup with KPL-404 dosed at 1, 5 or 10 mg/kg intravenously (IV) and KLH/TT antigens administered intramuscularly (IM) in 6 different groups with 7 animals/group over 56 day period
Arrows indicate timepoints for collection of serum/blood samples for **PK**, **TO**, **Anti-KLH/TT**, and **ADA**
*KLH dosed on day 1 instead of day 0
ADA, anti-drug antibody; Anti-KLH/TT, anti-keyhole limpet hemocyanin and tetanus toxoid; d, day; IM, intramuscular; IV, intravenous; PK, pharmacokinetics; TO, target occupancy

Figure 3: Flow Cytometric Analysis to Determine KPL-404 TO



*Representative histograms
Blood sample collected for TO was split into two tubes for analysis by flow cytometry. Cells were stained with CD20 PerCP-Cy5.5 and either CD40 specific C40/1605 AF647 or G28.5 AF647
Data was analyzed by first gating on lymphocytes then CD20+ B cells to examine %cells positive for CD40. C40/1605 competes with KPL-404 for binding to CD40 and positive staining is observed only in the absence of KPL-404 indicating % cells with free CD40. G28.5 binds CD40 in the absence or presence of CD40 indicating % all cells expressing CD40. KPL-404 occupied CD40 (TO) was calculated using indicated formula

RESULTS

Groups 1 – 4 (Figure 4, 5)

- KPL-404 PK
  - Serum concentrations peaked at 25, 135 and 270 mcg/mL and remained elevated 2, 3, and 4 weeks after first dose for 1, 5, and 10 mg/kg groups respectively
  - KPL-404 was cleared more rapidly after the second dose on d28 in 1 and 5 mg/kg dose groups
- KPL-404 TO
  - Complete (100%) CD40 TO was observed in all animals up to 1, 2, and 4 weeks in 1 , 5, and 10 mg/kg dose groups respectively
  - CD40 TO was lost more rapidly following the second dose on d28 in 1 mg/kg (<7 days) and 5 mg/kg (7 days) animals
- KPL-404 ADA
  - Presence of ADAs was confirmed in KPL-404-dosed animals (0 mg/kg: 7/7; 5 mg/kg: 4/7; and 10 mg/kg: 3/7 by d28), which would cause more rapid clearance of drug following second KPL-404 dose, consistent with observed PK and TO profiles
  - ADA positive animals were excluded from analysis of KLH and TT specific antibody titers
- KPL-404 effect on Ag-specific Ab titers
  - Suppression of primary anti-KLH and -TT IgM responses was observed in 1, 5, and 10 mg/kg dosed animals with greater suppression at 5 and 10 mg/kg compared to control animals
  - Primary anti-KLH and -TT IgG was suppressed in 5 and 10 mg/kg dosed animals compared to control animals
  - Secondary anti-KLH and anti-TT IgG response was suppressed in 5 mg/kg group compared to control animals
- CXCL13 levels, a biomarker of GC activity, was suppressed in 5 and 10 mg/kg dosed animals compared to control

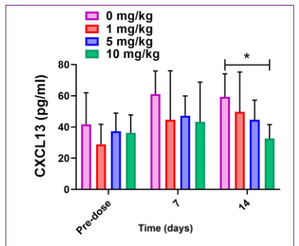
Groups 5 – 6 (Figure 6)

- KPL-404 PK: Serum KPL-404 peaked at 39 mcg/ml and remained elevated for 3 weeks
- KPL-404 TO: Complete CD40 TO was observed in all animals for 2 weeks
- KPL-404 effect on Ag-specific Ab titers: Secondary anti-KLH IgG recall response was suppressed compared to control animals

Figure 4: KPL-404 Shows Favorable Pharmacokinetic (PK) and Pharmacodynamic (PD) Profiles at 5 and 10 mg/kg doses (Groups 1-4)

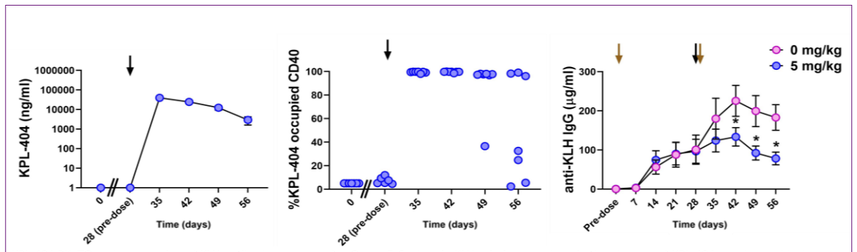
KPL-404 PK, TO and suppression of KLH and TT antibody responses wherein each column corresponds to 0 (pink symbols), 1 (red symbols), 5 (blue symbols) and 10 mg/kg (green symbols) groups (Groups 1-4)
Black arrows indicate KPL-404 dose and brown arrow indicates KLH/TT administration. ADA positive animals are indicated by ☒ in TO plots and excluded from analysis in KLH/TT antibody titers
Data represent mean±SEM; *p<0.05 compared to 0 mg/kg

Figure 5: KPL-404 Inhibits Serum CXCL13 at 10 mg/kg



Serum CXCL13 was detected by ELISA in samples from Groups 1-4
Data represent mean ± SEM
* p<0.05 relative to 0 mg/kg

Figure 6: KPL-404 Suppresses Secondary KLH IgG Recall Response Even After KPL-404-absent Antigen Priming



KPL-404 PK, TO and suppression of KLH antibody responses for Group 5-6 wherein KLH priming was done in the absence of KPL-404 are shown; black arrows indicate KPL-404 dose and brown arrow indicates KLH administration
Data represent mean ± SEM
*p<0.05 compared to 0 mg/kg

CONCLUSIONS

KPL-404 showed favorable pharmacokinetic (PK) and pharmacodynamic (PD) profiles, including engagement of CD40 target and blocking of antigen-specific primary and secondary antibody responses in a T-cell dependent antibody response model (even in presence of monkey ADAs to a humanized antibody, which are not unexpected) thus supporting further study of KPL-404 in treatment of autoimmune disease

DISCLOSURES: This research was conducted in conjunction with Altasciences Preclinical Seattle LLC and Burleson Research Technologies Inc and was funded by Kiniksa Pharmaceuticals, Ltd.
Presenting author, Sujatha Muralidharan, is an employees of Kiniksa Pharmaceuticals Corp. †Formerly at Kiniksa Pharmaceuticals Corp.