DWP212525, a novel JAK3 and Tec family kinase inhibitor, has the ability to reduce the severity of PV disease through autoantibody inhibition

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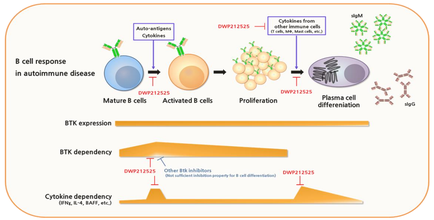
BACKGROUND



Pemphigus Vulgaris (PV) is a rare but life-threatening autoimmune blistering disease of the skin and mucous membranes. In PV patients, Anti-desmoglein3 (DSG3) antibody has significant correlation with disease activity. B cell is the main regulators which rise to plasma cells and produce autoantibody. Therefore, the anti-CD20 antibody Rituximab, which depletes B cells has been approved, and a small molecule BTK inhibitor is currently under development for the treatment of PV diseases. A representative BTK inhibitor, PRN1008, is undergoing phase 3 clinical trials for PV disease. BTK mediate BCR signaling in certain context of B cells and plays an important role in B cell proliferation. However, for plasma cell differentiation, the interaction between cells and cytokine signals is essential. Therefore, single BTK inhibitors such as Evobrutinib and Fenebrutinib did not show significant reduction of collagen antibodies in the CIA model, a representative model of autoimmune disease. We developed a novel, highly potent, and selective covalent inhibitor of JAK3 and TFK (Tec family kinase), DWP212525. Here, we report that DWP212525 can ameliorate pemphigus vulgaris by reducing autoantibody production followed by inhibiting T and B cells through JAK3/TFK inhibition.

METHODS

The inhibitory activity of DWP212525 upon JAK3 and TFK and the selectivity of DWP2125 against Cys family kinase members were evaluated by a series of biochemical assays. Immunophenotying was performed to define the inhibitory effect of DWP212525 upon T/B cell subtypes including Th1, 2, 17, Tfh, memory B cell and plasma cell, employing hPBMC under distinct conditions for each population. In addition, T cell dependent antibody response (TDAR) assay using NP-KLH was performed to confirm the dual inhibition of T and B cell. Furthermore, the efficacy of orally administered DWP212525 was evaluated in a PV mouse model via the disease severity and the level of anti-DSG3 antibody.

RESULTS

DWP212525 selectively inhibits JAK3/TFK

Kinase	Biochemical IC_{50} (nM) [a]	Selectivity (Fold)
JAK3	0.2	- *
JAK1	95	> 100*
JAK2	129	> 100*
TYK2	14	70*
BTK	1.2	- **
ITK	1.3	1.0 **
BMX	0.6	0.5**
TEC	2.3	2.0**
EGFR	65	54**
Cellular activity	**Biochemical IC_{50} (nM) [a]**	**Selectivity (Fold)**
pBTK (Ramos/Pervanadate)	11	-
pEGFR (A431/hEGF)	> 5,000	> 455#

- We selected DWP212525 based upon kinome assay.
- DWP212525 showed high potency against JAK3 and TEC family kinase including BTK, ITK.
- Binding of TYK2 is not relevant at therapeutic doses and is reversible

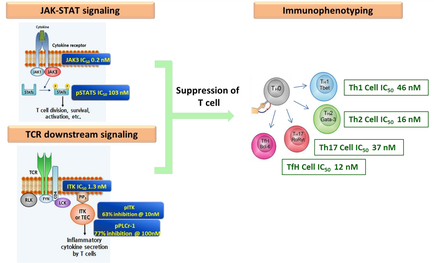
[a] *In-house data*

* *compared to JAK3*

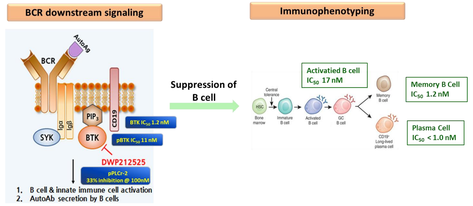
** *compared to BTK*

\# *compared to pBTK*

DWP21252 effectively inhibited T, B cell activation and differentiation

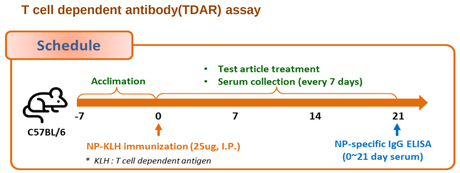


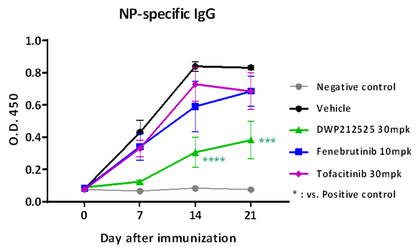
- DWP212525 inhibits JAK-STAT & TCR signaling and autoreactive T cell
- DWP212525 shows successful inhibition of Th2 and follicular helper T cells



- DWP212525 inhibits BCR signaling and autoreactive B cell
- DWP212525 inhibited plasma cell differentiation at concentrations <1.0 nM

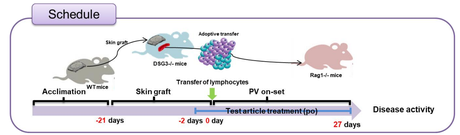
DWP212525 can fully repress T cell dependent antibody response

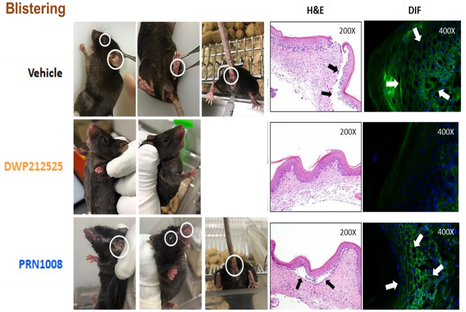


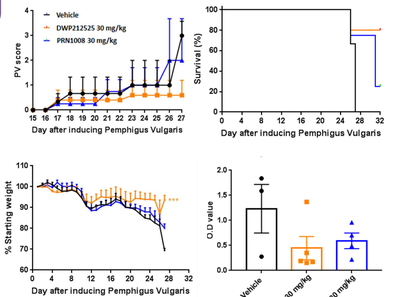


- DWP212525 has inhibitory effect in antigen-specific antibody formation by simultaneous JAK3 and TFK inhibition.
(vs. single target inhibitors)

DWP212525 is efficacious in a mouse PV model

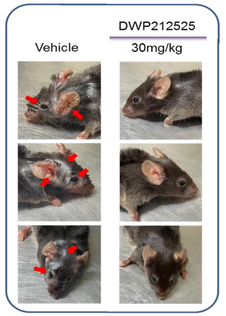


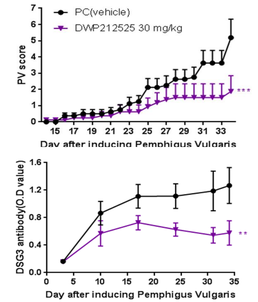




- In mouse PV model, DWP212525 alleviated the severity of disease index score prevented body weight loss and confirmed that the survival rate was higher than the positive control group treated with a BTK inhibitor and the vehicle group.
- DWP212525 showed anti-DSG3 antibody inhibition effect compared to BTK single inhibitor, PRN1008.

DWP212525 inhibit the production of autoantibody from the early stages o the disease.





- Depending on dosage, DWP212525 reduces disease severity and inhibit the production of autoantibody from the early stages of the disease.
(PV score & anti-DSG3 antibody)

CONCLUSIONS

- We developed a novel, highly potent, and selective covalent inhibitor of JAK3 and TFK, DWP212525.
- DWP2125255 showed potent inhibitory effects in Th2, Tfh and plasma cells.
- TDAR assay showed that DWP212525 effectively inhibits antibody production by simultaneously inhibiting T cells and B cells compared to single inhibitors.
- DWP212525 was confirmed that clinical symptoms and DSG3 antibodies were effectively reduced in mouse PV disease models.
- These results suggest that DWP212525 could be a promising treatment agent for PV patients through autoantibody inhibition.

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