nature portfolio

Peer Review File

Development of PVTX-405 as a potent and highly selective molecular glue degrader of IKZF2 for cancer immunotherapy

Corresponding Author: Professor Shaomeng Wang

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors describe the discovery of a series spiro-azo, oxo-alkane IKZF2 IMiDs which show potent IKZF2 degradation in HEK293 cells degradation. The solve an X-ray crystal structure of CRBN/IKZF2 of their lead compound 5 and use this structure to rationalize the SAR of the compounds described in the manuscript. Additional SAR leads to advance lead 16a (PVTX-405) which is profiled in Jurkat cells for degradation and functional activity. Compound 16a compares favorably to the Novartis IKZF2 compound DKY-709 (3), which was profiled in Phase 1 clinical trials, across the cellular assays.

Oral in vivo PK/PD assessment of 16a using 100% PEG200 as the dosing vehicle shows increasing dose proportional plasma, spleen and thymus exposures and increasing IKZF2 degradation with increasing exposure across these three tissues. In vivo efficacy is seen in a syngeneic MC38 xenograft model when dosed PO (100% PEG200) @ 30 mpk: 68% TGI over 3 weeks. Combination studies with 30 mpk of 16a with Anti-PD1 and Anti-LAG3 Abs also show a benefit compared to dosing with any single agent with respect to tumor growth and % survival.

I feel the authors have presented a solid data package showing the potential use of IKZF2 degradation to derepress Treg cells and activate Teff to treat solid tumors in combination with IO Abs and I support publication in Nature Communications but only after the following issues are addressed.

P5. The authors discuss that a major limitation of DKY-709 is the degradation of SALL4 which has been shown to lead to teratogenic effects. However, the patient population suitable for treatment with an IKZF2 IMiD would likely not be impacted by a teratogenic drug. The authors should remove the statement that SALL4 degradation is a limitation of DKY-709.

P5. The authors state that a hERG IC50: 7.1 μM could be an issue with DKY-709. This would only be an issue if there was > 50% hERG inhibition at 300x the efficacious free plasma exposure. Thus, without that data, the authors should remove the hERG inhibition statement for DKY-709.

P8. The authors describe the studying the effects the calculated pKa of the basic amines in their analogs on IKZF2 degradation. However calculated pKa are notoriously inaccurate unless they've been parametrized with a training set of experimental data of similar compounds. Thus, if the authors want to discuss pKa effects, they should generate measure pKa data for compounds 5, 11 and 12.

P9. The authors should explain why 5 shows > 100% bioavailability in mouse. Is there evidence of enterohepatic recirculation, metabolic saturation on dosing?

Vehicle used for the in vivo studies with 16a: It appears that all in vivo studies done with 16a use 100% PEG200 as a PO dosing vehicle, something that is far from an FDA approved human clinical dosing formulation. My guess is that 16a has poor aqueous solubility and shows little dose proportional exposure in a more traditional aqueous oral formulation. In my view, this really the limits of the utility of 16a being close to a clinically developable agent. The authors should discuss why they used 100% PEG200 as the dosing vehicle and report the aqueous solubility of 16a in Table 5.

I would l like the authors to report an in vitro cellular assay to MC38 xenograft PK/PD study so that the reader can understand the in vitro to in vivo exposure degradation correlation between the assays. This will require:

- Jurkat cells: unbound (free) IKZF2 DC50
- MC38 model: unbound (free) tumor exposure levels; IKZF2 degradation at the timepoints when tumor exposure is assessed

It's important to run this study as the MC38 xenograft shows partial regression and it will help the reader understand what needs to be optimized in 16a to achieve a superior compound.

Reviewer #2

(Remarks to the Author)
Overall the manuscript describes a high impact discovery.
In the introduction section the authors should reference the selective IKZF2 degrader PLX-4545, which is reportedly in clinical development https://www.australianclinicaltrials.gov.au/
The structure, in vitro and preclinical in vivo activity of PLX-4545 has been publicly disclosed recently (American Chemical Society Fall Meeting 2024: K. Freeman-Cook "Discovery of PLX-4545, a molecular glue degrader of IKZF2" Aug 21st 2024)
The statement is the Summary section "... PVTX-405 is a potent, highly selective, and orally efficacious molecular glue 26 degrader of IKZF2 and represents the most promising IKZF2 degrader identified to date" should be modified, as there is no basis to define what "most promising" means.

Reviewer #3

(Remarks to the Author)

This study developed an IKZF2-specific MG degrader, PVTX-405, for targeting Treg cells to enhance immune checkpoint therapies. Comparisons between PVTX-405 and Phase I DKY709 (Novartis) demonstrate that PVTX-405 not only has good efficacy and potency but also significantly better specificity, likely reducing the teratogenic effects associated with SALL4 degradation. Although the development process of the 5-12 derivatives appears retrospective, the final characteristics of PVTX-405 are impressive. The study shows the comprehensive preclinical investigations of PVTX-405.

Minor points/comments:

1. Is PVTX-405 ready for clinical trials? If not, are there any disadvantages of this compound that the authors did not mention in the manuscript?

2. page 3 introduction "Interestingly, selective depletion of IKZF2 in CD4 Tregs caused destabilization of Tregs residing in the TME only, not in peripheral lymphoid tissue."
Page5 "A single, oral administration of PVTX-405 was capable of inducing profound and persistent depletion of IKZF2 protein in spleen and thymus tissues in humanized CRBN mice."
Can the authors discuss/explain the different effects caused by IKZF2 depletion compared to IKZF2 degradation via PVTX-405? And are there any notable side effects associated with PVTX-405?

3. 16a (PVTX-405) versus 16b: 16b is also potent and highly active (DC50 = 4.1 nM, Dmax = 89%). Its much weaker affinity to CRBN (IC50 = 1335 nM) could be considered an advantage, as it reduces interference with CRBN's native substrates. A review paper titled "Lessons from Natural Molecular Glue Degraders" (PMID: 38864421) discusses this idea in detail. 16b may be a valuable candidate for the next generation of MG degraders that lack inhibitory activity.

4. The effects shown in Figure 6C appear to be marginal.

5. The ligand fit with the electron density map needs to be shown to evaluate the quality of the ligand model in the complex.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Prior review questions have been adequately addressed. Publish as is.

Reviewer #3

(Remarks to the Author)
My questions/concerns have been addressed by the authors, and I have no further questions.

REVIEWER COMMENTS and Our Response to Each and Every Point

Reviewer #1 (Remarks to the Author):

The authors describe the discovery of a series spiro-azo, oxo-alkane IKZF2 IMiDs which show potent IKZF2 degradation in HEK293 cells degradation. The solve an X-ray crystal structure of CRBN/IKZF2 of their lead compound 5 and use this structure to rationalize the SAR of the compounds described in the manuscript. Additional SAR leads to advance lead 16a (PVTX-405) which is profiled in Jurkat cells for degradation and functional activity. Compound 16a compares favorably to the Novartis IKZF2 compound DKY-709 (3), which was profiled in Phase 1 clinical trials, across the cellular assays.

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Response: We thank Reviewer #1 for the very positive comments of our manuscript and the critical insights. We have made revisions to address each point.

P5. The authors discuss that a major limitation of DKY-709 is the degradation of SALL4 which has been shown to lead to teratogenic effects. However, the patient population

suitable for treatment with an IKZF2 IMiD would likely not be impacted by a teratogenic drug. The authors should remove the statement that SALL4 degradation is a limitation of DKY-709.

P5. The authors state that a hERG IC50: 7.1 μM could be an issue with DKY-709. This would only be an issue if there was > 50% hERG inhibition at 300x the efficacious free plasma exposure. Thus, without that data, the authors should remove the hERG inhibition statement for DKY-709.

Response: We agree with the reviewer that, without published clinical trial data for DKY709, it is difficult to definitively determine whether SALL4 degradation activity and hERG inhibition pose limitations for its clinical development. Nonetheless, we would like to emphasize that the SALL4 degradation and hERG inhibition for DKY709 reflect its off-target activities, hence presenting an opportunity to develop best-in-class IKZF2 degraders with an improved selectivity profile.

We have modified the paragraph to read as below:

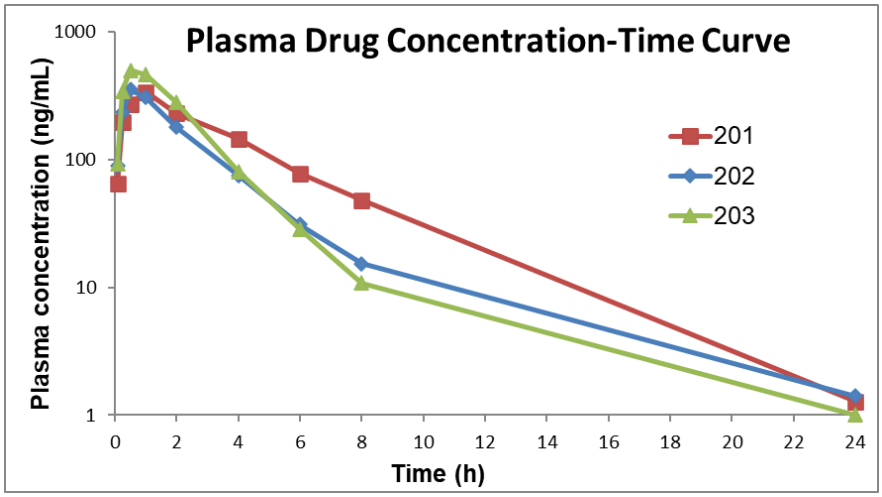
"However, detailed characterization of DKY709 in our study (Table 2) identified several pharmacological properties that warrant optimization: DKY709 significantly degraded the neo-substrate SALL4 (DC_{50} = 4.9 nM, D_{max} = 55%), which has been linked to teratogenic effects;[36-38] and demonstrated moderate hERG inhibition (IC_{50} = 7.1 μM). These findings highlight the potential to discover a potent and highly selective IKZF2 degrader with improved pharmacology by minimizing the off-target activities associated with DKY-709."

P8. The authors describe the studying the effects the calculated pKa of the basic amines in their analogs on IKZF2 degradation. However calculated pKa are notoriously inaccurate unless they've been parametrized with a training set of experimental data of similar compounds. Thus, if the authors want to discuss pKa effects, they should generate measure pKa data for compounds 5, 11 and 12.

Response: The pKa value of "0.4 unit" on Page 8 was removed. Instead, we revised the manuscript to indicate the electron withdrawing effect on the basicity of the nitrogen atom in the piperidine ring and the effect on IKZF2 degradation.

*P9. The authors should explain why **5** shows > 100% bioavailability in mouse. Is there evidence of enterohepatic recirculation, metabolic saturation on dosing?*

Response: Examination of oral PK data for individual animals showed variabilities between animals, which are common for oral administration in PK studies (see Reviewer Response Figure 1 and Reviewer Response Table 1). While one animal showed >100% of oral bioavailability, two other animals displayed oral bioavailability close to 100%. We now have provided detailed PK data for each animal in a Supplementary Table 1. Hence, 108% of oral bioavailability simply indicated that compound **5** has ~100% of oral bioavailability.



Reviewer Response Figure 1: Oral PK of Compound 5 in individual animal.

Reviewer Response Table 1: PK parameters of compound 5 in individual animals.

G2 Animal No.	**Administration Route**	**Dose Level** mg/kg	$T_{1/2}$ h	T_{max} h	C_{max} ng/mL	$AUC_{(0-t)}$ h*ng/mL	F %
201	PO	3.0	3.04	1.00	339.50	1646.00	134.32
202	PO	3.0	4.24	0.50	355.26	1057.14	86.27
203	PO	3.0	1.38	0.50	500.52	1269.61	103.60
n		3	3	3	3	3	3
G2-Mean		3.0	2.89	0.67	398.42	1324.25	108.06
G2-SD		0.0	1.44	0.29	88.77	298.21	24.33

Vehicle used for the in vivo studies with 16a: It appears that all in vivo studies done with 16a use 100% PEG200 as a PO dosing vehicle, something that is far from an FDA approved human clinical dosing formulation. My guess is that 16a has poor aqueous solubility and shows little dose proportional exposure in a more traditional aqueous oral formulation. In my view, this really the limits of the utility of 16a being close to a clinically developable agent. The authors should discuss why they used 100% PEG200 as the dosing vehicle and report the aqueous solubility of 16a in Table 5.

Response: Since 100% PEG200 is a good solubilizer and generally considered safe to animals, it is a common dosing formulation for evaluation of small molecule drugs in animals. In our initial *in vivo* evaluation of PVTX-405 using 100% PEG200 as the dosing vehicle, PVTX-405 demonstrated an excellent pharmacokinetic profile in mice. We then consistently used 100% PEG200 as the oral formulation to study the PK/PD and efficacy of PVTX-405 in mouse models.

In fact, PVTX-405 was found to have good aqueous solubility, which is now included in Table 5 in the revised manuscript (Reviewer Response Table 2 below). Based upon its excellent aqueous solubility, it is expected that the clinical development of PVTX-405 will employ an oral capsule or an oral tablet.

Reviewer Response Table 2: The solubility data of test compounds and control compound in SGF, SIF, FeSSIF and FaSSIF

Compound ID	Solubility in SGF (μM)	Solubility in SIF (μM)	Solubility in FeSSIF (μM)	Solubility in FaSSIF (μM)
Diclofenac	7.46	320.39	303.45	324.30
PVTX-405 (16a)	319.43	318.47	283.70	304.82
16b	301.96	294.68	320.15	175.16

I would l like the authors to report an in vitro cellular assay to MC38 xenograft PK/PD

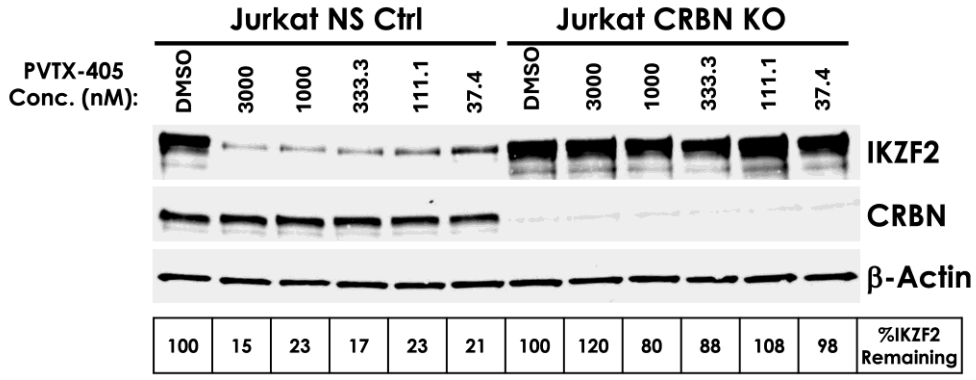
study so that the reader can understand the in vitro to in vivo exposure degradation correlation between the assays. This will require:

- Jurkat cells: unbound (free) IKZF2 DC50

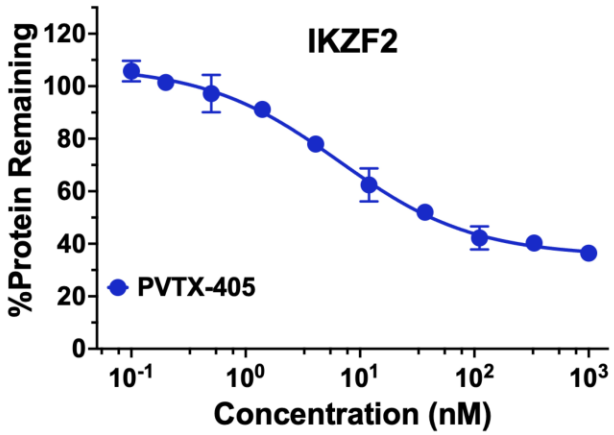
- MC38 model: unbound (free) tumor exposure levels; IKZF2 degradation at the timepoints when tumor exposure is assessed

It's important to run this study as the MC38 xenograft shows partial regression and it will help the reader understand what needs to be optimized in 16a to achieve a superior compound.

Response: We thank the reviewer for these insightful questions. IKZF2 degradation in Jurkat cells is shown in Figure 5 of the manuscript. Densitometry analysis of the Western blot data indicates a DC_{50} of <37.4 nM (Reviewer Response Figure 2). Additionally, we further evaluated PVTX-405 using an IKZF2 FACS assay in Jurkat cells with 16 hours of treatment, which yielded a DC_{50} of 6.3 nM. The DC_{50} value for PVTX-405 obtained using an IKZF2 FACS assay in Jurkat cells is similar to the DC_{50} value observed in human Tregs (DC_{50} = 6 nM, Figure 6B). This data has now been included in the manuscript as Figure 4A (Reviewer Response Figure 3).



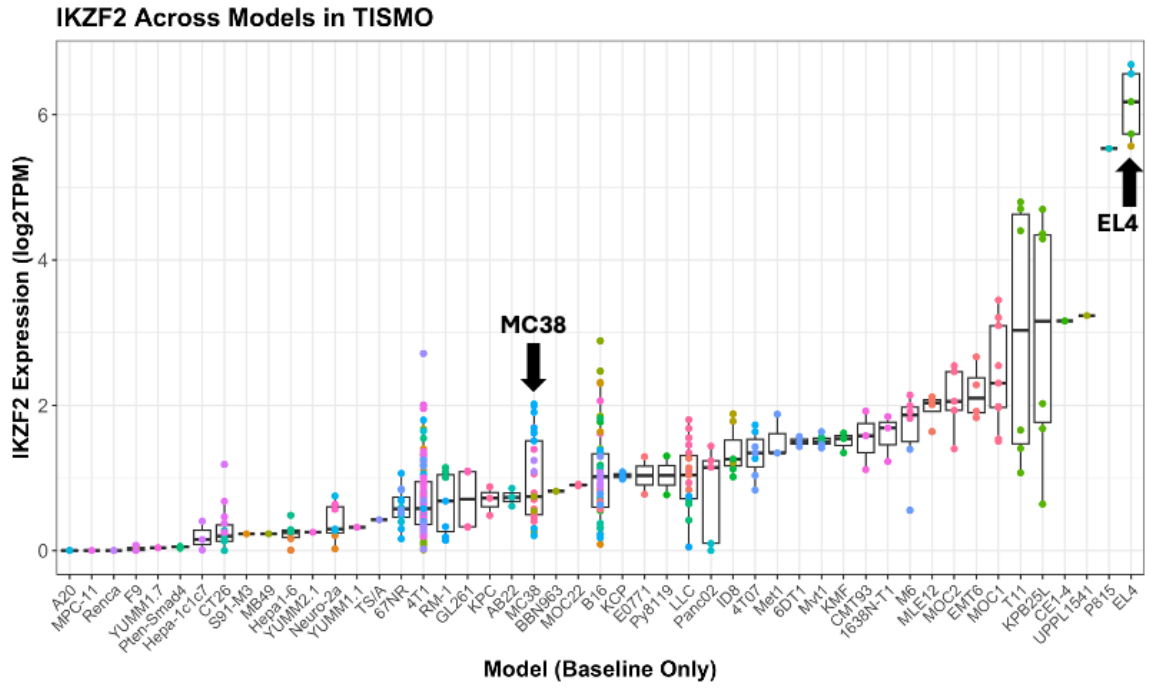
Reviewer Response Figure 2: WB analysis shows that CRISPR/Cas9 mediated KO of CRBN in Jurkat cells completely abrogates IKZF2 degradation by PVTX-405. Densitometry analysis of data suggest that in CRBN expressing Jurkat cells DC50 is <37.4 nM.



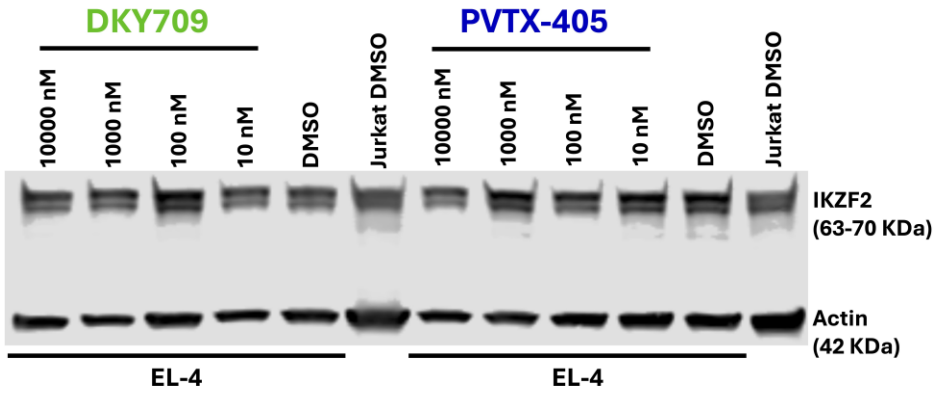
Reviewer Response Figure 3: FACS analysis showing rapid degradation of IKZF2 in Jurkat cells after PVTX-405 treatment for 16 hrs.

We have not evaluated IKZF2 degradation in MC38 cells for two main reasons: (1) It is well-established that CRBN-based molecular glue degraders do not degrade neo-substrates in mouse cells due to a difference in the thalidomide-binding domain (TBD) of CRBN at amino acid residue 391[1, 2], and thus we did not expect to observe IKZF2 degradation by PVTX-405 in mouse cell lines; and (2) IKZF2 expression is predominantly restricted to T-cells beyond the developmental stage. Hence MC38 colon cancer cells are unlikely to express IKZF2. Subsequently we looked at publicly available database of syngeneic mouse tumor models[3] and identified a mouse T-lymphoblast cell line EL-4 (ATCC, Catalog # TIB-39) as potential model of choice with highest IKZF2 expression (IKZF2 expression, log2TPM of ~6, Reviewer Response Figure 4A) amongst all available mouse models to evaluate effect of PVTX-405 and DKY709 on mouse IKZF2. Our data confirmed the previous observation that CRBN-based molecular glue degraders, such as PVTX-405 and DKY709, do not degrade CRBN neo-substrates, including IKZF2, in mouse cells (Reviewer Response Figure 4B).

(A)



(B)

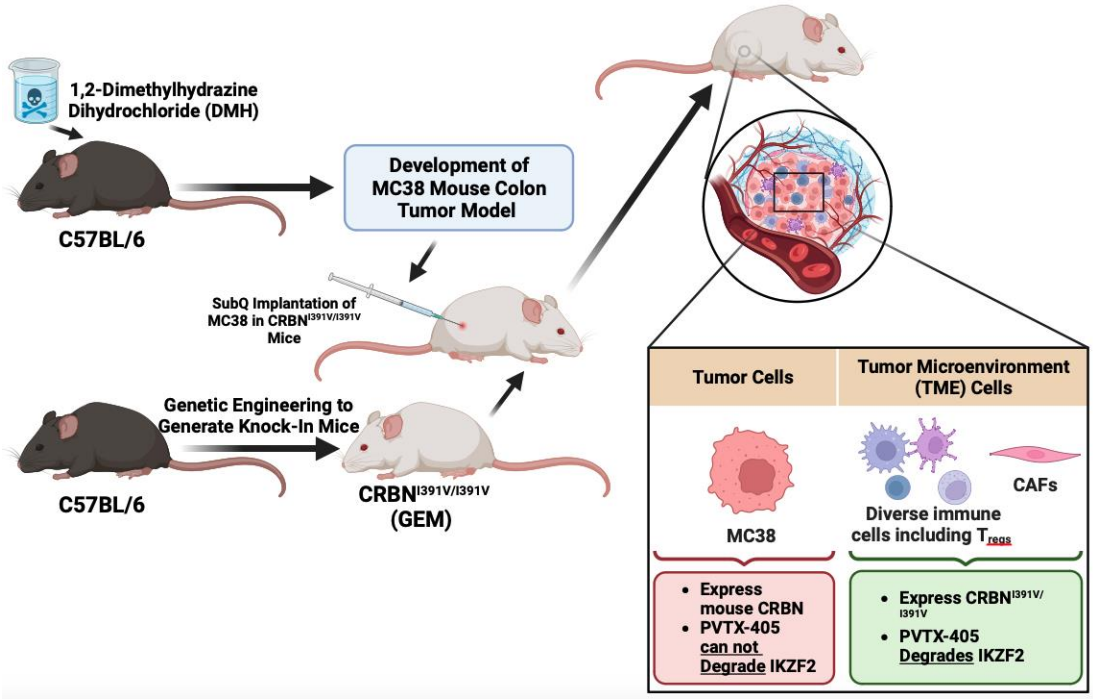


Reviewer Response Figure 4: (A) Expression of IKZF2 across 49 syngeneic mouse tumor models (data downloaded from TISMO database, http://tismo.cistrome.org). Each dot represent separate study data. IKZF2 expression in MC38 and EL-4 is highlighted with black arrow. (B) WB showing effect PVTX-405 and DKY709 on mouse IKZF2 in EL-4 cells after 16 hrs of treatment.

Given that CRBN-based glue degraders are ineffective in mouse cells, the *in vivo* efficacy observed in the MC38 xenograft model is likely attributable to the impact of PVTX-405 on systemic and TME-resident Tregs in CRBN^{I391V} (humanized CRBN) mice. Prior study by Nakagawa et. al.[4] has also demonstrated that selective depletion of IKZF2 in CD4+ Tregs enhances antitumor immunity in the MC38 model. As depicted in the schematic of

the MC38 xenograft model in CRBN^{I391V} mice (Reviewer Response Figure 5), only TME cells, including Tregs within MC38 tumors, express the CRBN^{I391V} variant capable of mediating PVTX-405-induced IKZF2 degradation. Since T-cells constitute only a small subset of TME cells, directly assessing target engagement in MC38 tumors would not be feasible. Therefore, we did not measure drug exposure or IKZF2 degradation in the tumors. Instead, we assessed these parameters in the spleen and thymus, which contain abundant T-cells and exhibit robust IKZF2 expression.

As shown in Figure 7, an oral dose of 30 mg/kg (the *in vivo* efficacious dose) achieved a C_{max} of 1926 ng/g (~3.66 µM) in the spleen and 413 ng/g (~786 nM) in the thymus. Considering the plasma protein binding of PVTX-405 in mice (93.4%), the maximum unbound concentrations were approximately 39.2 nM in the spleen and 8.4 nM in the thymus. These concentrations are ~6-fold and ~1.4-fold higher, respectively, than the observed DC_{50} values of ~6 nM in Jurkat cells (*in vitro*) and human Tregs (*ex vivo*). This data demonstrates a strong correlation between the degradation potency observed *in vitro* and *ex vivo* with the *in vivo* degradation potency and efficacy of PVTX-405.



Reviewer Response Figure 5: Schematic showing details of MC38 syngeneic xenograft model in CRBN^{I391V} mice.

Reviewer #2 (Remarks to the Author):

Overall the manuscript describes a high impact discovery. In the introduction section the authors should reference the selective IKZF2 degrader PLX-4545, which is reportedly in clinical development https://www.australianclinicaltrials.gov.au/ The structure, in vitro and preclinical in vivo activity of PLX-4545 has been publicly disclosed recently (American Chemical Society Fall Meeting 2024: K. Freeman-Cook "Discovery of PLX-4545, a molecular glue degrader of IKZF2" Aug 21st 2024)

Response: We thank Reviewer #2 for the very positive comments of our manuscript and the critical insights. We have revised the manuscript to address each point.

We agree with the reviewer that *in vitro* and *in vivo* pharmacology data of PLX-4545 was recently disclosed in ACS conference. However, the disclosure was only in the form of presentation and actual pharmacology data are not publicly available so we are not able to make direct comparisons of their pharmacological properties of PLX-4545 and PVTX-405. However, we have edited the paragraph on page 4 to include the sentence about PLX-4545.

"Two selective IKZF2 degraders, DKY709 and PLX-4545 (Figure 1) have entered Phase 1 clinical trials as novel cancer immunotherapy.[34-35] Bonazzi et al. described the discovery of a selective molecular glue degrader of IKZF2, DKY709 (Figure 1), which does not induce degradation of the other neo-substrates, including IKZF1/3, GSPT1 and CK1α.[34]"

The statement is the Summary section "... PVTX-405 is a potent, highly selective, and orally efficacious molecular glue 26 degrader of IKZF2 and represents the most promising IKZF2 degrader identified to date" should be modified, as there is no basis to define what "most promising" means.

Response: We have now revised the summary statement as follows: "Taken together, PVTX-405 is a potent, highly selective, and orally efficacious molecular glue degrader of IKZF2. Indeed, PVTX-405 has been selected as an advanced preclinical candidate to be

developed as a novel immunomodulatory agent for the treatment of human cancers alone or in combination with ICTs."

Reviewer #3 (Remarks to the Author):

This study developed an IKZF2-specific MG degrader, PVTX-405, for targeting Treg cells to enhance immune checkpoint therapies. Comparisons between PVTX-405 and Phase I DKY709 (Novartis) demonstrate that PVTX-405 not only has good efficacy and potency but also significantly better specificity, likely reducing the teratogenic effects associated with SALL4 degradation. Although the development process of the 5-12 derivatives appears retrospective, the final characteristics of PVTX-405 are impressive. The study shows the comprehensive preclinical investigations of PVTX-405.

Response: We thank Reviewer #3 for the very positive comments of our manuscript and the critical insights. We have revised the manuscript to address each point.

Minor points/comments:

1. Is PVTX-405 ready for clinical trials? If not, are there any disadvantages of this compound that the authors did not mention in the manuscript?

Response: Based upon our extensive preclinical data, PVTX-405 has been selected for IND-enabling studies. Once the IND-enabling studies are completed, we plan to evaluate PVTX-405 in human clinical trials. There are no known disadvantages identified for PVTX-405 in all of our studies.

2. page 3 introduction "Interestingly, selective depletion of IKZF2 in CD4 Tregs caused destabilization of Tregs residing in the TME only, not in peripheral lymphoid tissue." Page5 "A single, oral administration of PVTX-405 was capable of inducing profound and persistent depletion of IKZF2 protein in spleen and thymus tissues in humanized CRBN mice."
Can the authors discuss/explain the different effects caused by IKZF2 depletion compared

to IKZF2 degradation via PVTX-405? And are there any notable side effects associated with PVTX-405?

Response: We thank the reviewer for the question. Based on the available data, it is currently challenging to directly compare the effects of genetic knockdown of IKZF2 in CD4+ Tregs with PVTX-405-mediated systemic IKZF2 degradation. We observed comparable tumor regression in the MC38 model treated with PVTX-405 and in MC38 tumors grown in mice with IKZF2-depleted CD4+ Tregs, which suggests that the phenotypic outcome associated with degradation is similar to genetic depletion[4]. However, we have not yet examined differences in the functional status of systemic Tregs versus TME-resident Tregs, as described in the PNAS article by Nakagawa et al.[4], as this is beyond the scope of our current study. Importantly, in our preclinical efficacy studies conducted in humanized CRBN ($CRBN^{I391V}$) mice, we did not observe any adverse effects associated with prolonged systemic IKZF2 degradation over the duration of the entire study.

3. 16a (PVTX-405) versus 16b: 16b is also potent and highly active (DC50 = 4.1 nM, Dmax = 89%). Its much weaker affinity to CRBN (IC50 = 1335 nM) could be considered an advantage, as it reduces interference with CRBN's native substrates. A review paper titled "Lessons from Natural Molecular Glue Degraders" (PMID: 38864421) discusses this idea in detail. 16b may be a valuable candidate for the next generation of MG degraders that lack inhibitory activity.

Response: We agree with the reviewer that 16b may be a very interesting degrader based upon its weak binding to CRBN and potent and effective degradation of IKZF2. However, the observed potent IKZF2 degradation induced by **16b,** the *R*-enantiomer of **16a**, is likely due to its fast chiral conversion to the active *S*-enantiomer **16a** in cell culture media after 6 hours incubation in the HiBiT degradation assay. In comparison, in evaluation of their binding affinities of **16a** and **16b** to CRBN, the incubation time was only 1 hr, which would afford much less chiral conversion due to a shorter incubation time. We evaluated the conversion of **16b** to **16a** during a monkey PK study using both intravenous and oral administration and found that there was only ~20% of conversion of **16b** to **16a** over 24 h (data not shown), suggesting a slow conversion *in vivo*. In addition, we found that there

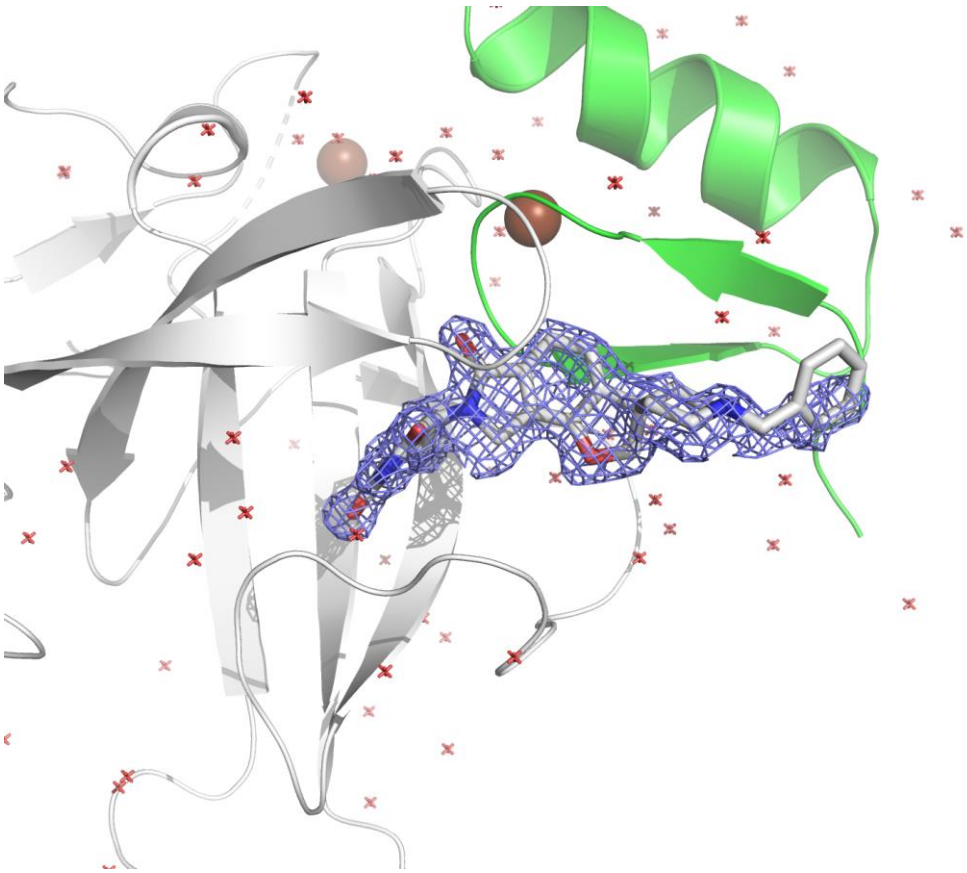
was no chiral conversion when **16a** was stored in solid form, indicating that **16a** has an excellent chemical stability (data not shown). For these reasons, we chose to carry out extensive evaluations of **16a** (PVTX-405).

4. The effects shown in Figure 6C appear to be marginal.

Response: We agree with the reviewer that the effect on effector T-cells in the co-culture assay with Tregs (Figure 6C) appears to be relatively small. *Ex vivo* Treg assays, while valuable for studying regulatory T cell (Treg) function, have several limitations when interpreted in the context of immuno-oncology. These include the inability to fully replicate the complexity of the tumor microenvironment, potential artifacts introduced during Treg isolation, variability in Treg subsets, lack of antigen specificity in most assays, and challenges in capturing the dynamic nature of Treg function *in vivo*.[5-7] Such limitations may lead to highly variable responses across different donors in *ex vivo* Treg assay. Nevertheless, in our study we did observe statistically significant increase ($p = 0.0312$) in proliferation of effector T-cells in Treg co-culture assay when treated with PVTX-405.

5. The ligand fit with the electron density map needs to be shown to evaluate the quality of the ligand model in the complex.

Response: We agree with the reviewer. We have now provided the image below of the density for one of the 4 molecules in the asymmetric unit (Reviewer Response Figure 6). The density is of similar quality for each of the 4 copies.



Reviewer Response Figure 6: 2Fo-Fc electron density for compound 5 contoured at 1.0 sigma.

Additional Note

During the preparation of source data file for the revised manuscript, we identified errors in the reported DC_{50} and D_{max} values for Compounds **5**, **13**, **14**, and **15** obtained using IKZF2 HiBit assay. These errors occurred because data from a less sensitive assay were inadvertently used and incorrectly transferred to the main version of the manuscript for these compounds in the first version of the manuscript submitted for review. We have corrected these values in the revised manuscript. Importantly, these corrections do not affect the interpretation, conclusions, or overall flow of the manuscript. In addition to

addressing the reviewers' comments, we have made these adjustments to ensure the accuracy and integrity of the data presented. We sincerely apologize for this oversight and appreciate your understanding.

References

1. Fink, E. C. et al. CrbnI391V is sufficient to confer in vivo sensitivity to thalidomide and its derivatives in mice. *Blood* **132**, 1535-1544 (2018).

2. Gemechu, Y. et al. Humanized cereblon mice revealed two distinct therapeutic pathways of immunomodulatory drugs. *Proc. Natl. Acad. Sci. USA* **115**, 11802-11807 (2018).

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7. Whiteside, T. L. Human regulatory T cells (Treg) and their response to cancer. *Expert Rev. Precis. Med. Drug Dev.* **4**, 215-228 (2019).