VXL100, a MUC1 Signal Peptide based Immunotherapy, Acts Through a Neoantigen-like Mechanism, and Shows Promising Effects in Hematological Cancers

Limor Chen, Michael Y. Shapira and Riva Kovjazin; Abstract 8413

Vaxil Biotherapeutics Ltd, Ness Ziona, Israel and Hadassah Medical Center, Jerusalem, Israel

INTRODUTION

VXL100 (ImMucin®), a 21mer peptide, derived from the MUC1 signal peptide (SP) domain, has been shown to be safe and to elicit a robust and specific T and B-cell responses in stable and progressive multiple myeloma patients in a phase I/II clinical trial[1].

The low avidity of signal peptides as antigens, is believed to result in escaping negative selection in the thymus during development, and preservation of active clones[2]. Thus, it is expected that the baseline level of specific T-cells against this antigen, in both naïve healthy individuals, and more so, in cancer patients with MUC1 positive tumors, will trigger a robust and specific anti-tumor response upon vaccination with the peptide. Additionally, the exceptionally high density of MHC class I and II epitopes in signal peptides, as revealed by our VaxHit platform[3] makes these peptides better vaccine candidates than other domains.

To prove the neoantigenic properties of MUC1 SP, we set to test endogenous levels of specific anti-VXL100 T-cells by staining for VXL100-specific or control multimers. We also performed proliferation assays for patient's TIL and normal donors' PBMC, using cells stimulated with VXL100 or peptides from other MUC1 antigenic domains, i.e., from the Cytoplasmic Tail (CT) and from the Tandem Repeat Array (TRA).

METHODS

Samples from >18 years old healthy donors or VXL100-naïve hematology patients, treated in the BMT unit at Hadassah Medical Center were collected. The study was conducted in compliance with the principles of the International Conference on Harmonisation guidelines on Good Clinical Practice, the Declaration of Helsinki and local regulatory requirements.

PATIENT NO.	DIAGNOSIS	GENDER	AGE
1	MM	F	72
2	Lymphoma	F	78
3	Lymphoma	F	76
4	MM	M	61
5	MM	F	79
6	MM	M	76
7	MM	M	67
8	MM	M	59
9	Plasmacytoma	M	53
10	MM	M	72
11	Lymphoma	F	52
12	ALL	F	62
13	MM	M	56
14	MM	F	52
15	MM	M	58
16	MM	M	52
17	MM	F	66
18	MM	F	52

Table 1: basic profile of enrolled patients

RESULTS

Figure 1

VXL100 is a storng antigen eliciting a response in naive individuals

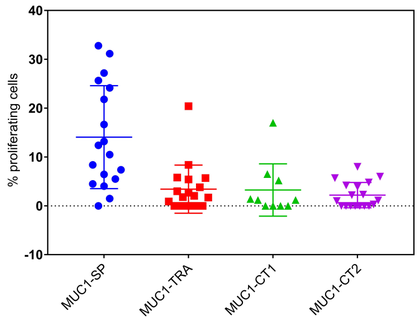


Figure 2

MUC1 specific T-cells are abundant in hematological patients

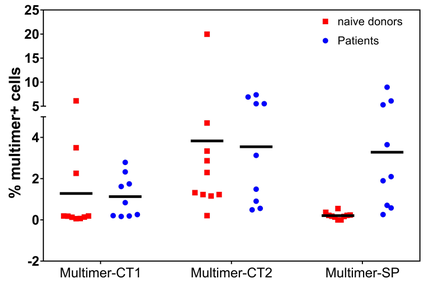


Figure 3

Naive healthy individuals are highly reactive to VXL100

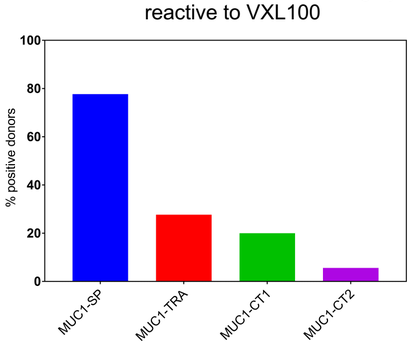


Figure 4

Exhausted anti-MUC-SP clones are rare in hematology patients

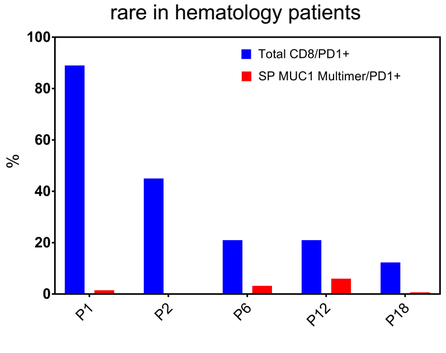


Figure 5

MUC1-SP-specific T-Cells are correlated to antigen expression on tumor cells

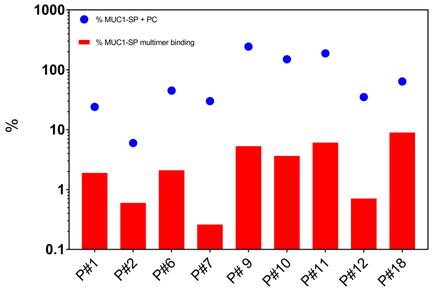
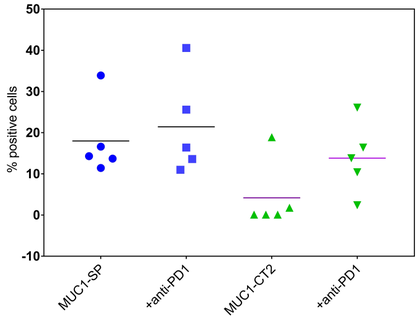
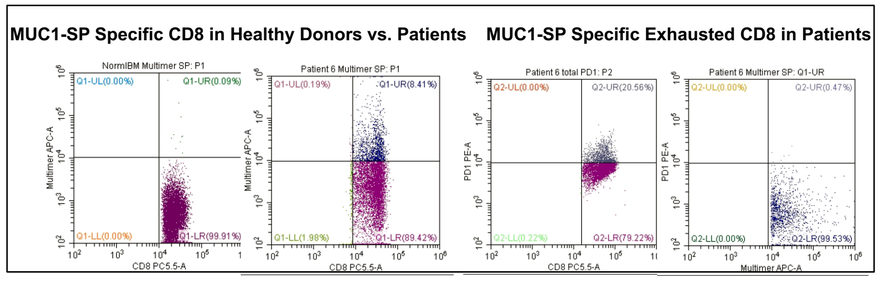


Figure 6

MUC1-SP-specific exhausted T-cells are infrequent compared to others



Representative Data



SUMMARY

- VXL100 specific T-cell were found in 100% of untreated patients (1.3-6%), VS. 0% in normal donors (Fig2).
- A correlation was observed between the MUC1 signal peptide expression levels on tumor cells and levels of endogenous VXL100 specific T-cells (Fig 5).
- VXL100-specific exhausted CD8 cells exist at a non-significant levels as compared to the total exhausted CD8 (Fig 4).
- PBMC from 70% of normal donors. and 94% of untreated cancer patients showed a strong proliferative response to VXL100 stimulation. Conversely, when stimulated with control peptides, 0.5% - 5.2% of untreated patients and 0 - 13% of donors showed positive proliferation response (Fig 1).

CONCLUSIONS

- MUC1-SP is a superior antigen able to evoke a significant cellular response in naïve individuals.
- Hematological patients positive for MUC1-SP, harbor highly reactive clones, able to respond to VXL100 stimulation promptly.
- These clones are exceptionally fit, showing a low level of the "exhausted" phenotype
- VXL100 demonstrates several features of a true neoantigen.
- **It is an excellent candidate for the development of novel immunotherapy schemes in combination with synergizing modalities.**

REFERENCES

1. Carmon L. et al. Br J Haematol. 2015 Apr;169(1):44-56 Journal Article, *Name of Journal*
2. P. Marrack and J.W. Kappler, Cold Spring Harb Perspect Med. 2012 Sep 1;2(9)
3. Kovjazin R. et al. Mol Immunol. 48. 1009-1018 (2011)

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