

Interview with



DR. JING WATNICK
CO-FOUNDER & CEO



DR. LOU VAICKUS
INTERIM CHIEF MEDICAL OFFICER



PharmaShots ViewPoints Interview:

Vigeo Therapeutics' Dr. Lou Vaickus and Dr. Jing Watnick Share Insights on VT1021 Data Presented at SITC 2020

In a recent interview with PharmaShots, **Dr. Jing Watnick, Co-Founder and Chief Executive Officer, and Dr. Lou Vaickus, Interim Chief Medical Officer at Vigeo** shared their views on the data findings presented at the **SITC 2020 Annual Meeting** that demonstrated **VT1021** as a single-agent has a favorable safety profile and shows early signals of clinical activity across a wide variety of solid tumors, including pancreatic cancer and glioblastoma

Shots:

- VT1021 is a first-in-class, dual-modulating therapy that blocks the CD47 immune checkpoint and activates CD36, stimulating cytotoxic T-cell functions, inducing apoptosis in tumor and endothelial cells, and increasing the phagocytosis of the tumor by M1 macrophages by stimulating the production of Tsp-1
- The compound initially targets pancreatic cancer, glioblastoma multiforme (GBM) and ovarian cancer
- Vigeo Therapeutics is open for collaborations to advance its clinical program and build pipeline

Tuba: Can we have a glimpse of the poster presented at the Society for Immunotherapy of Cancer's (SITC) 2020 Annual Meeting?

A first-in-human Phase 1/2 open label trial evaluating the safety, pharmacology, and preliminary efficacy of VT1021 in subjects with advanced solid tumors

Abstract 374 Devilingam Malingam¹, Weel Herb², Anita Patnaik³, Susanna Utharans⁴, Marrett Akhanna⁵, Mariah R. Patel⁶, Abhin Dasari⁷, Andrea Bullock⁸, Patrick Wern⁹, Shubham Patel¹⁰, Mary Mulycahy¹¹, Robert Outendoff¹², Randolph Watnick¹³, Lou Vaickus¹⁴, Melissa Vincent¹⁵, Suning Wang¹⁶, Marsha Crochens¹⁷, Michael Cieslewicz¹⁸, and Jing Watnick¹⁹

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The immunosuppressive nature of the tumor microenvironment (TME) is a major barrier to the effective treatment of many cancer patients. Immunosuppression in the TME is mediated by multiple cell types, including myeloid derived suppressor cells (MDSCs), M2 macrophages, and regulatory T cells (Tregs). Vigeo is addressing this critical unmet need by developing VT1021, a cyclic peptide derived from proscapsin that induces the expression of thrombospondin-1 (TSP-1) in MDSCs that are recruited to the TME (Kang et al. 2009; Calnan et al. 2015; Wang et al. 2016). Preclinical studies of VT1021 have shown robust anti-tumor activity in multiple animal models of ovarian, pancreatic, and breast cancer. The induction of TSP-1 in MDSCs reprograms the TME from one that is immunosuppressive and tumor-promoting, to one that activates the adaptive immune system and is tumor-inhibiting. Specifically, TSP-1, via binding to the cell surface receptors CD36 and CD47 to induce apoptosis in tumor and endothelial cells, blocks the "do-not-eat-me" signal, increases the M1/M2 macrophage ratio, and activates cytotoxic T lymphocytes (CTLs) (Kang et al. 2010; Zhang et al. 2009; Russell et al. 2015). High levels of CD36 or CD47 are each poor prognostic indicators for many types of cancers (Ehwa et al., 2018; Huang et al., 2020) and there are currently no drugs that target both molecules simultaneously. These characteristics make VT1021 a first-in-class agent and led to the initiation of this first-in-human study.

VT1021 Modulates the TME via CD36 and CD47

VT1021 modulates the TME via CD36 and CD47
VT1021 reprograms the TME from one that is immunosuppressive to one that is immunotherapeutic. The immunosuppressed tumor immune microenvironment (TIME) is characterized by high levels of Tregs, M2 tumor-associated macrophages (M2 TAMs) and MDSCs. VT1021 binds to a receptor on MDSCs and induces expression of TSP-1. TSP-1 binding to one of its receptors, CD36, inhibits angiogenesis, induces apoptosis in tumor cells, endothelial cells and Tregs, and increases M1 macrophage adhesion, survival, and the M1/M2 ratio. TSP-1 binding to its other major receptor, CD47, blocks the "do-not-eat-me" signal allowing macrophage phagocytosis of tumor cells and increases CTL infiltration and activity resulting in tumor cell death.

Contact
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Background
The immunosuppressive nature of the tumor microenvironment (TME) is a major barrier to the effective treatment of many cancer patients. Immunosuppression in the TME is mediated by multiple cell types, including myeloid derived suppressor cells (MDSCs), M2 macrophages, and regulatory T cells (Tregs). Vigeo is addressing this critical unmet need by developing VT1021, a cyclic peptide derived from proscapsin that induces the expression of thrombospondin-1 (TSP-1) in MDSCs that are recruited to the TME (Kang et al. 2009; Calnan et al. 2015; Wang et al. 2016). Preclinical studies of VT1021 have shown robust anti-tumor activity in multiple animal models of ovarian, pancreatic, and breast cancer. The induction of TSP-1 in MDSCs reprograms the TME from one that is immunosuppressive and tumor-promoting, to one that activates the adaptive immune system and is tumor-inhibiting. Specifically, TSP-1, via binding to the cell surface receptors CD36 and CD47 to induce apoptosis in tumor and endothelial cells, blocks the "do-not-eat-me" signal, increases the M1/M2 macrophage ratio, and activates cytotoxic T lymphocytes (CTLs) (Kang et al. 2010; Zhang et al. 2009; Russell et al. 2015). High levels of CD36 or CD47 are each poor prognostic indicators for many types of cancers (Ehwa et al., 2018; Huang et al., 2020) and there are currently no drugs that target both molecules simultaneously. These characteristics make VT1021 a first-in-class agent and led to the initiation of this first-in-human study.

Study Design
This study is a first-in-human, phase 1/2, open-label, multicenter, dose escalation (Part 1) and expansion (Part 2) study in advanced, refractory, solid tumors.
Part 1 (Dose Escalation): 28 subjects were used to determine the MTD and RP2D for expansion. The RP2D was not reached. The RP2D was determined to be 10 mg/kg based on several factors: 1) safety of the RP2D and 2) the dose-limiting and above the RP2D PK exposure were similar to 10 mg/kg and 15 mg/kg dose, profile was similar to other strong cycles, though there were more observable immunotoxicity prior to the next dose, and the rate of observed AEs in preclinical models. 3) clinical parameters where doses at and below the RP2D continued preclinical PK markers.
Part 2 (Expansion): ~100 subjects with one of the following indications will be enrolled: Pancreatic Cancer, Glioblastoma, and a basket cohort with High CD36 and High CD47-expressing cancers.

Clinical Outcome (escalation cohort; 28 evaluable subjects)
Preliminary Efficacy in dose escalation cohort:
Out of 28 evaluable subjects, one subject achieved partial response (rhynchoma, 432x days on study), 11 subjects had durable stable disease (SD) in 9 different solid tumors, with a disease control rate (DCR) of 43%. More importantly, 8 of 12 PRSDs had high CD36 AND high CD47 expression with an average duration of 185 days on study (as of 10/1/20).

PK Profile (escalation)
All 28 evaluable patients in the dose escalation cohort 28 completed cycle 1 (3x/21 days), 1 subject is ongoing in cycle 2. 11 subjects discontinued due to adverse events.
The mean observed AEs were grade 1 or 2 (majority 10%), while 10/28 subjects had grade 3 or 4 AEs. The most common AEs were grade 3 or 4 (majority 10%), while 10/28 subjects had grade 3 or 4 AEs. The most common AEs were grade 3 or 4 (majority 10%), while 10/28 subjects had grade 3 or 4 AEs.

TME Reprogramming
VT1021 Reprograms the TME by inducing TSP-1 expression, increasing CTL infiltration, and increasing the M1/M2 ratio in a Subject with Metastatic Renal Cell Carcinoma. The expression of several biomarkers of TME-mediated immunosuppression in both pre- and in-treatment biopsies. The level of CD36 and CD47 expression was maintained during treatment. MDSC levels were not demonstrably affected by treatment with VT1021 and pre-treatment biopsies had significantly elevated TSP-1 levels compared to pre-treatment. Consistent with the increase in TSP-1 and the reprogramming of MDSCs, VT1021 induced a dramatic increase in M1 macrophages as well as the ratio of M1/M2 macrophages, accompanied by increased infiltration of CTLs and an increase in the ratio of CTLs/Tregs.

Safety Profile (escalation cohort)
Drug-related Treatment Emergent Adverse Events
Treatment Overview Emergent Adverse Events

Conclusion
Across all doses tested, VT1021 was found to be safe and very well tolerated, with dose proportional PK properties. The data from the escalation cohort demonstrated the ability of VT1021 to induce TSP-1 resulting in the dramatic reprogramming of the TME, as evidenced by augmented levels of active tumor-killing immune cells and lower levels of immunosuppressive cells. VT1021 treatment resulted in a high overall disease control rate (43%), which was further augmented in subjects whose tumors expressed high levels of both CD36 AND high CD47 (DCR 75%).

Presented at the 2020 SITC Annual Conference
Study is sponsored by Vigeo Therapeutics, Inc.
Clinical trial information: NCT03364400

Tuba: Highlight the key points of the VT1021 development program and its mechanism of action.

Lou: *VT1021 is a first-in-class, dual-modulating compound that blocks the CD47 immune checkpoint and activates CD36, stimulating cytotoxic T-cell functions, inducing apoptosis in tumor and endothelial cells, and increasing the phagocytosis of the tumor by M1 macrophages by stimulating the production of thrombospondin-1 (Tsp-1). Vigeo is developing VT1021 as a therapeutic agent across a range of cancers, with a current focus on solid tumors.*

Tuba: Describe in brief about the specific disease targets of VT1021.

Lou: *Currently the target indications for VT1021 are pancreatic cancer, glioblastoma multiforme (GBM) and ovarian cancer. Vigeo is also targeting patients with tumors that express high levels of both CD47 and CD36 as a biomarker based/indication agnostic strategy.*

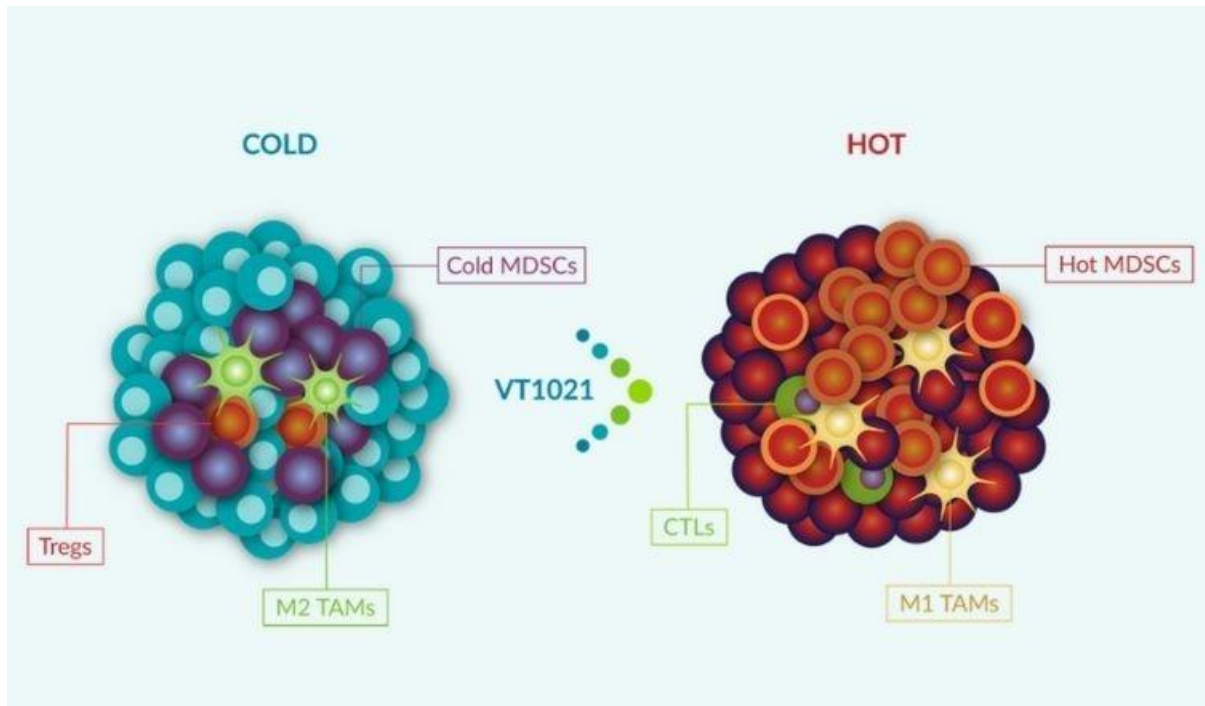
Tuba: Discuss the key findings from the interim clinical data from the P-I/II study of VT1021.

Lou: *Dual modulation of CD47 and CD36 promotes complementary anti-tumor activity as 75% of patients who achieved a PR or SD had high expression of both CD47 and CD36 prior to entering the study.*

Tuba: When can we expect the complete results of the P-I/II study and initiation of P-II study?

Lou: *Escalation has been completed and expansion is expected to be completed by 2Q of 2021. We expect to initiate combination studies in 2Q of 2021.*

Tuba: What are the unique attributes about Vigeo's lead candidate VT1021?



Lou: *Vigeo's lead asset, VT1021, is a first-in-class dual modulating compound that blocks the CD47 immune checkpoint and activates CD36, which induces apoptosis and increases the M1:M2 macrophage ratio. VT1021 achieves this through stimulation of thrombospondin-1 (Tsp-1). The goal of these dual-modulating effects is conversion of immuno-suppressive, or "cold," tumors that don't respond to immuno-oncology agents, to immuno-stimulated, or "hot," tumors that are potentially more receptive to immuno-oncology agents. Vigeo is developing VT1021 as a therapeutic agent across a range of cancers, with a current focus on solid tumors. Pre-clinical results have demonstrated that single-agent VT1021 causes tumor regression at both the primary and metastatic sites.*

Tuba: What were the major highlights about the dose escalation portion of first in human trial with VT1021?

Lou: *The dose escalation study was marked by a very clean safety profile, an expected and dose dependent pharmacokinetic profile, and the attainment of changes in desired biomarkers in patients that were predicted in nonhuman animal models. As such the recommended Phase 2 dose was determined based on a combination of safety, pharmacokinetic, and pharmacodynamic parameters. Additionally, there was a very*

overall high disease control rate (SD+PR) of 43% (12/28). When analyzing patients with high levels of both CD36 and CD47, the disease control rate increased to 80% (8/10).

Tuba: How do you feel about the development status of VT1021 so far?

Lou: *We are very encouraged by the development of the biomarker-based strategy and feel that this will significantly impact the clinical development of VT1021. Early results in the indication expansion cohorts are promising and we are cautiously optimistic. In addition, the clean safety profile allows for combinability with other immunomodulatory and chemotherapy drugs.*

Tuba: What are the other programs that we can expect to escalate further from Vigeo's pipeline?

Lou: *There are several preclinical-stage programs in the pipeline focusing on TME modulation.*

Tuba: Do you plan for any partnerships for the commercialization strategies of VT1021?

Lou: *We are continuously evaluating potential partnerships and remain open to any number of possibilities as we work to advance our clinical program and build out our pipeline.*

About Authors:



Dr. Jing Watnick is a co-founder of Vigeo and leads the company as its CEO. She has over 20 years of experience in the pharmaceutical industry, including roles in program and portfolio management, strategic planning, business development, alliance management, and preclinical and clinical research.



Lou Vaickus serves as Interim CMO of Vigeo. He has over 30 years of experience that began as an academic scientist, then practicing physician, then spanned into industry with preclinical, clinical, and globally marketed pharmaceutical products.

About Interviewer:



Tuba Khan is Senior Editor at PharmaShots. She is curious, creative, and passionate about recent updates and innovation in the Life sciences industry. She covers Biopharma, MedTech, and Digital health segments. Tuba also has an experience of digital and social media marketing and runs the campaigns independently. She can be contacted on tuba@pharmashots.com