

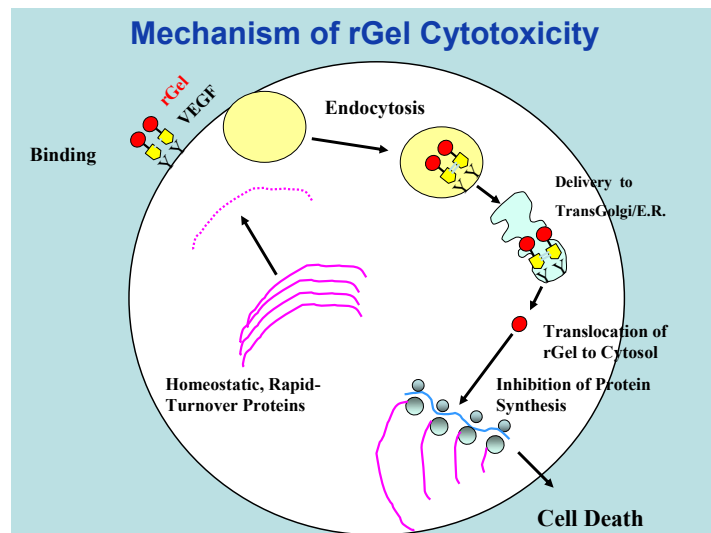
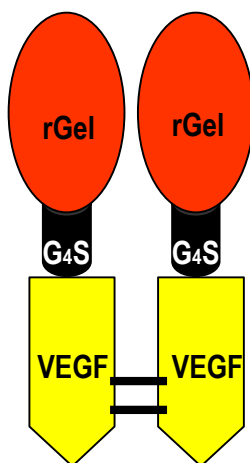
## VEGF/rGel

Indications: Ocular Neovascular Diseases

Stage: Advanced Pre-clinical

**VEGF/rGel** (VEGF121/rGel) is a vascular disruptive agent being developed for the treatment of bone metastases, multiple solid tumors and ocular diseases including wet age-related macular degeneration (AMD) and diabetic retinopathy. VEGF/rGel is a fusion protein, which targets and ablates osteoclast precursor macrophage cells through a VEGFR1-mediated mechanism. It also targets and ablates solid tumor microvasculature through a VEGFR2 (KDR)-mediated mechanism, without harming normal vasculature.

VEGF/rGel is comprised of full-length human Vascular Endothelial Growth Factor (VEGF121), which retains full functionality for receptor interaction, tethered via a flexible G4S linker to toxin payload recombinant Gelonin (rGel). It can be readily manufactured inexpensively and efficiently in *E. coli* fermenters. Recombinant gelonin (rGel) is a 30-kDa single chain protein that inactivates the 28S ribosomal subunit via a well-defined molecular mechanism.



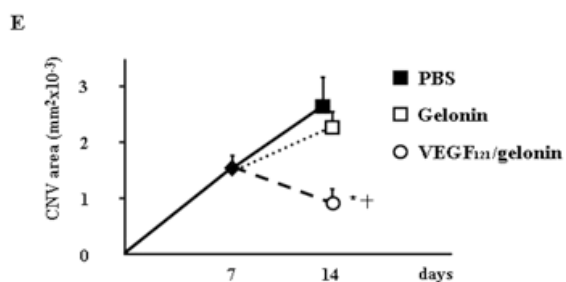
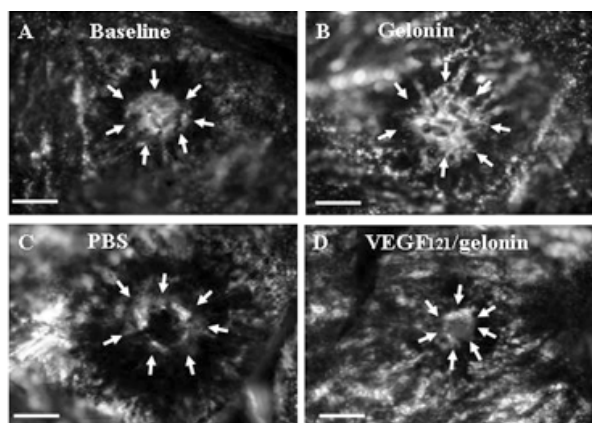
### Preclinical Development

Animal studies using VEGF/rGel have been completed for ocular disorders:

- Diabetic Retinopathy (DR)
- Age-related Macular Degeneration (AMD)

*Preclinical milestones completed:*

- Pre-IND package completed and submitted to FDA.
- Pre-IND Guidance Call held with FDA: reached agreement on pre-clinical and clinical issues.
- Additional work required by FDA (<\$100K) initiated and ~50% completed.
- Phase I clinical protocol approved by MDACC Institutional Review Board (IRB).
- MDACC Clinical Principal Investigator and team recruited and ready to proceed.
- Contract Manufacturing Organization (CMO) selected and detailed inspection completed.
- Manufacturing Process Instructions (MPI's) completed and ready for transfer to CMO.



### **Intravenous injection of VEGF/rGel causes regression of choroidal neovascularization**

The area of choroidal neovascularization at rupture sites appeared substantially smaller in mice that had been injected with VEGF/rGel (D, arrows) than that in mice that had been injected with rGel (B, arrows) or PBS (C, arrows). It was also smaller than the amount of choroidal neovascularization seen at baseline (A).

*In animal models, VEGF antagonists are very good at suppressing growth of neovascularization and reducing excessive leakage but they fail to cause regression of new vessels (K. Takahashi and P. A. Campochiaro, unpublished data). This is supported by observations in patients with choroidal neovascularization treated with VEGF antagonists in whom leakage is reduced, but the choroidal neovascularization is not eliminated. Regression of neovascularization is likely to be needed to achieve optimal results. Systemic or intraocular administration of VEGF/rGel to achieve regression of neovascularization combined with a VEGF antagonist to prevent recurrence is an appealing strategy that deserves investigation. Ref: Akiyama et al 2005*

### **VEGF/rGel - poised for clinical development**

- VEGF/rGel is well-expressed in bacterial systems
- VEGF/rGel is a homodimer-84 kDa
- Both the VEGF and rGel proteins are biologically active in the fusion construct
- VEGF/rGel is specifically cytotoxic to cells expressing flk-1 receptors
- VEGF/rGel is cytotoxic to both log-phase and confluent cells over expressing flk-1 receptors
- VEGF/rGel localizes in tumor neovasculature
- The MTD of VEGF/rGel is ~ 40 mg/kg
- Active in macular degeneration and diabetic retinopathy
- Useful imaging agent for patient selection
- Phase I studies carried out at MD Anderson on another gelonin fusion, HuM195/rGel have demonstrated the safety of gelonin in humans.

## Intellectual Property

Our US patent was allowed in October 2011

CLFR:251

**TITLE:** VASCULAR TARGETING OF OCULAR NEOVASCULARIZATION

**Summary:** Methods and compositions for treating eye diseases with polypeptide fusion molecules. Fusion molecules deliver toxins, pro-apoptotic sequences and/or anti-angiogenic sequences to cells via a VEGF targeting moiety. (FF)

Client Reference No.: NULL

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	Country	Case	Status	Application No.	Filing Date	Patent No.
1	Canada	PCT National Phase	Exam requested	2606989	04/28/2006	
2	European Patent Office	PCT National Phase	Published	06751936.3	04/28/2006	
3	Japan	PCT National Phase	Exam requested	2008-509219	04/28/2006	
4	United States of America	National	Published	11/414782	04/28/2006	
5	United States of America	Provisional	Expired	60/675958	04/29/2005	
6	Patent Cooperation Treaty	Ordinary PCT Application	Expired	PCT/US2006/016496	04/28/2006	

## Reference:

Mol Pharmacol. 2005 Dec;68(6):1543-50. Epub 2005 Sep 8.

**Vascular targeting of ocular neovascularization with a vascular endothelial growth factor121/gelonin chimeric protein.**

Akiyama H, Mohamedali KA, E Silva RL, Kachi S, Shen J, Hatara C, Umeda N, Hackett SF, Aslam S, Krause M, Lai H, Rosenblum MG, Campochiaro PA.

### Abstract

Tumors provide an extremely abnormal microenvironment that stimulates neovascularization from surrounding vessels and causes altered gene expression within vascular cells. Up-regulation of vascular endothelial growth factor (VEGF) receptors has allowed selective destruction of tumor vessels by administration of a chimeric protein consisting of VEGF121 coupled to the toxin gelonin (VEGF/rGel). We sought to determine whether there is sufficient up-regulation of VEGF receptors in endothelial cells participating in ocular neovascularization to permit a similar strategy. After intravenous injection of 45 mg/kg VEGF/rGel, but not uncoupled recombinant gelonin (rGel), there was immunofluorescent staining for rGel within choroidal neovascularization in mice and regression of the neovascularization occurred, demonstrating successful vascular targeting via the systemic circulation. Intraocular injection of 5 ng of VEGF/rGel also caused significant regression of choroidal neovascularization and regression of retinal neovascularization in two models, transgenic mice with expression of VEGF in photoreceptors and mice with ischemic retinopathy, whereas injection of 5 ng of rGel had no effect. These data suggest that the strategy of vascular targeting can be applied to nonmalignant neovascular diseases and could serve as the basis of a new treatment to reduce established ocular neovascularization.