**A Method for Regulating Angiogenesis by ApoB Modulation**

**Methods of Regulating Angiogenesis by Administering Agents Which Modulate Apob-100 Polypeptide Levels**

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| **Project Number:** | 1621 |
| **Principal Investigator:** | Dr. Karina Yaniv |
| **Patent Status:** | Pending |

**Overview**

**A novel method for treating angiogenesis related diseases or disorders by regulating the levels apolipoprotein B (ApoB)**

**Background and Unmet Need**

Angiogenesis is the formation of new blood vessels from pre-existing vasculature. Therefore, angiogenesis is a fundamental part of tissue development. ~~Angiogenesis is relevant to numerous non-neoplastic diseases such as macular degeneration, psoriasis, endometriosis, arthritis, and cardiovascular disease.~~ However, angiogenesis is also an important mechanism for the growth and metastasis of tumors. Tumor cells promote angiogenesis by secreting the signaling molecule VEGF (vascular endothelial growth factor) which binds to its respective receptor (VEGFR). Previous studies have shown that the vascular endothelial growth factor receptor 1 (VEGFR1) plays an inhibitory role in angiogenesis, acting as a “sink” for the VEGF ligand. **by manipulating VEGFR1, potential**

**The Technology**

The technology is based on the novel discovery, made in the lab of Dr. Karina Yaniv, that ApoB-containing lipoproteins regulate angiogenesis by modulating expression of VEGFR1 at the transcriptional level. Dr. Yaniv and her team have demonstrated *in vivo* in Zebrafish that ApoB is responsible for modulating angiogenesis by showing: (A) eliminating MTP (microsomal triglyerceride transfer protein) expression replicated previously reported pathological angiogenesis. (B) Injections of MTP mRNA into MTP deficient Zebrafish larvae repressed the angiogenesis phenotype. (C) Downregulation of ApoB recapitulated the angiogenesis of MTP deficient mutants. (D) Reduction of LDL concentrations in *wt* embryos using statins also reproduced the phenotype of excess angiogenesis seen in MTP mutants. Furthermore, the team has shown that angiogenic phenotypes seen in MTP mutants result from a direct response of endothelial cells to lipoprotein concentrations and not from alternative cues triggered by fatty-acid depletion. The addition of short-, intermediate- or long-chain fatty acids to the embryo culture media did not rescue the vascular phenotype.

The connection between ApoB levels and VEGFR1 transcription was further strengthened by demonstrating that injection of VEGFR1 mRNA to MTP mutants suppressed the angiogenesis phenotype. The team have also proved the ApoB inhibits VEGFR1 expression at the transcriptional level and not by destabilizing VEGFR1 mRNA. Lastly, the team were able to determine that the ApoB protein itself, and not the lipid moieties within the lipoprotein, acts on endothelial cells to regulate angiogenesis.

***Advantages and***

* A novel orthogonal method for treating pathological angiogenesis.
* Diagnosis of metastasized cancer by determining the levels of apo-B in a fluid sample (blood, plasma, saliva, urine, etc.)
* Repressing angiogenesis by directly adminstraing ApoB.

**Development Status**

The team of Dr. Yaniv have demonstrated *in vivo* in zebrafish models the effects of ApoB-containing lipoproteins on angiogenesis. Using this model they have shown that exogenous delivery of LDL inhibits angiogenesis. *In vitro,* treating human aortic endothelial cells (HAECs) and human umbilical vein endothelial cells (HUVECs) with LDL elicited an increase in VEGFR1 expression. The team have also shown in hyperlipidemic and Apoe- or Ldlr-null mice increased endothelial-specific VEGFR1 expression compared to control WT mice, confirming the connection between ApoB and VEGFR1 expression in higher vertebrates. This research has been published in the prestigious scientific journal of *Nature Medicine[[1]](#footnote-1)*.

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1. Avraham-Davidi, Inbal, et al. "ApoB-containing lipoproteins regulate angiogenesis by modulating expression of VEGF receptor 1." *Nature medicine* 18.6 (2012): 967. [↑](#footnote-ref-1)