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# A novel engineered VEGF blocker with an excellent pharmacokinetic profile and robust anti-tumor activity

Lily Liu[1], Haijia Yu[1], Xin Huang[2], Hongzhi Tan[3], Song Li[2], Yan Luo[1], Li Zhang[3], Sumei Jiang[3], Huifeng Jia[3], Yao Xiong[3], Ruliang Zhang[4], Yi Huang[3], Charles C Chu[5,6,7] and Wenzhi Tian[1*]

## Abstract

**Background:** Relatively poor penetration and retention in tumor tissue has been documented for large molecule drugs including therapeutic antibodies and recombinant immunoglobulin constant region (Fc)-fusion proteins due to their large size, positive charge, and strong target binding affinity. Therefore, when designing a large molecular drug candidate, smaller size, neutral charge, and optimal affinity should be considered.

**Methods:** We engineered a recombinant protein by molecular engineering the second domain of VEGFR1 and a few flanking residues fused with the Fc fragment of human IgG1, which we named HB-002.1. This recombinant protein was extensively characterized both *in vitro* and *in vivo* for its target-binding and target-blocking activities, pharmacokinetic profile, angiogenesis inhibition activity, and anti-tumor therapeutic efficacy.

**Results:** HB-002.1 has a molecular weight of ~80 kDa, isoelectric point of ~6.7, and an optimal target binding affinity of <1 nM. The pharmacokinetic profile was excellent with a half-life of 5 days, maximal concentration of 20.27 μg/ml, and area under the curve of 81.46 μg · days/ml. When tested in a transgenic zebrafish embryonic angiogenesis model, dramatic inhibition in angiogenesis was exhibited by a markedly reduced number of subintestinal vessels. When tested for anti-tumor efficacy, HB-002.1 was confirmed in two xenograft tumor models (A549 and Colo-205) to have a robust tumor killing activity, showing a percentage of inhibition over 90% at the dose of 20 mg/kg. Most promisingly, HB-002.1 showed a superior therapeutic efficacy compared to bevacizumab in the A549 xenograft model (tumor inhibition: 84.7% for HB-002.1 versus 67.6% for bevacizumab, $P < 0.0001$).

**Conclusions:** HB-002.1 is a strong angiogenesis inhibitor that has the potential to be a novel promising drug for angiogenesis-related diseases such as tumor neoplasms and age-related macular degeneration.

**Keywords:** VEGF inhibitor, VEGFR1, Recombinant Fc-fusion protein, Anti-tumor therapy, Angiogenesis

## Background

Targeted tumor therapy is the focus of recent intense drug development by the pharmaceutical industry with the primary interests centered on antibody drugs [1]. However antibody and/or recombinant protein drugs with molecular weights (MWs) of over 100 kDa usually have relatively poor tumor penetration and retention capacity for which the molecular size, charge, as well as target binding affinity play important roles [2]. There are several barriers to large molecule transport in solid tumors due to disordered vasculature, tissue structure, as well as extracellular matrix (ECM). These factors, which impact penetration and retention of large molecule drugs, have to be considered when designing new molecular constructs.

Angiogenesis, the process by which the existing vascular network expands to form new blood vessels, is mainly mediated by vascular endothelial growth factor (VEGF), which upon binding with VEGF receptor (VEGFR), can induce phosphorylation of the receptors expressed in the blood vessel endothelial cells [1], thus leading to proliferation of the endothelial cells and the development of the

* Correspondence: tian110602@huabobio.com
[1]Department of Cell Biology, Huabo Biopharm Co Ltd., Shanghai 201203, China
Full list of author information is available at the end of the article

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vascular system. Under pathological conditions, VEGF-A and other members of the VEGF family including placental growth factor (PlGF) are upregulated [3-6]. Among the factors contributing to angiogenesis, VEGF-A is the main ligand driving angiogenesis, making it an important target for drug development.

Several drugs targeting VEGF have been approved for use in the treatment of cancer [7] as well as for wet age-related macular degeneration (AMD) [8]. Bevacizumab is a humanized antibody targeting VEGF-A and was approved under the trade name of Avastin in 2004 for the treatment of metastatic colon cancer [9-11] as well as several other solid tumors including lung cancers [12,13], glioblastoma [14,15], renal cancers [16], and ovarian cancers [17-19]. The main mechanism by which bevacizumab exerts anti-tumor activity is by preventing VEGF-A from binding with its receptors, thus resulting in inhibition of new blood vessel growth in tumor tissues. Bevacizumab is a humanized IgG1 with over 90% of human and less than 10% of murine components [20]. The recommended dose for bevacizumab is 5 mg/kg every 2 weeks, even though it could be detected in serum for 12 weeks [21]. Bevacizumab is the first VEGF blocker proven to improve survival by 30% in patients with metastatic colorectal cancer [22]. However due to target limitation (only targeting VEGF-A) as well as relatively poor tissue penetration because of its large size, the overall impact of bevacizumab in prolonging survival was very limited [22,23], with 5-year survival generally between 5% and 8% [23], suggesting that VEGF-A blockade alone may not be good enough to completely prevent tumor angiogenesis and corresponding tumor growth.

Aflibercept (originally called VEGF-Trap) was approved in August of 2012 under the trade name of Zaltrap for the treatment of metastatic colon cancer, and the same molecule was approved in November of 2011 under the trade name of Eylea for the treatment of AMD. Aflibercept is a recombinant fusion protein consisting of the second immunoglobulin (Ig) domain of VEGFR1 and the third Ig domain of VEGFR2, fused to the immunoglobulin constant region (Fc) portion of human IgG1 [24]. Unlike bevacizumab, aflibercept exhibits affinity for all isoforms of VEGF and PlGF [25] and exerts robust antivascular effects by rapid regression of existing tumor vessels [26], normalization of surviving mature vessels [27], and inhibition of new tumor vessel growth [28]. The anti-tumor efficacy of aflibercept has been confirmed in several solid tumor models, all demonstrating effective tumor inhibition [29]. Aflibercept has a MW of 110 kDa and has a half-life in plasma of 4-5 days [24]. The clinical benefits for aflibercept treatment of metastatic colon cancer patients are similar to bevacizumab [30].

It has been documented that the VEGF-binding affinity of VEGFR1 is 10 fold higher than that of VEGFR2 [31] and the second Ig domain of VEGFR1 is critical for VEGF binding [32]. We reasoned that a recombinant protein composed of only the second domain (D2) of VEGFR1 might retain sufficient VEGF binding, but also have better bioavailability and penetration properties due to its smaller size as compared to the previously described current generation of drugs that block VEGF. We therefore designed an expression vector that expressed a recombinant protein consisting of the D2 portion of VEGFR1 fused with the Fc portion of human IgG1. This protein was extensively characterized for its target-binding affinity, angiogenesis inhibition, and pharmacokinetic (PK) profile, as well as for its anti-tumor efficacy in several xenograft tumor models.

## Methods

### Engineering of recombinant proteins

HB-002.1 is a recombinant protein consisting of two components: one is the D2 domain of human VEGFR1 (Flt1) (P134-T226) plus 5 (S129-R133) and 2 (N227, T228) amino acids of upstream and downstream flanking sequence respectively, and the second is the Fc fragment of human IgG1. To construct the HB-002.1 expression vector, 57 nucleotides encoding the signal peptide of mouse IgG1 heavy chain were added to the 5' end of VEGFR1-D2, a Kozak sequence was added to the 5' end of the signal peptide sequence, and cloning sites, *Hin*dIII and *Eco*RI, were added to the 5' and 3' ends of the resulting sequence, respectively. This designed D2 expression cassette sequence was synthesized (GenScript) and subcloned into the *Hin*dIII and *Eco*RI sites of the pHB-Fc vector (Generay, ID: X9913T).

The recombinant Flt1[2]-Fc protein contains the VEGFR1-D2 domain (P134-T226) without the addition of flanking region amino acids, plus the Fc fragment of human IgG1.

All recombinant proteins were expressed and purified from Chinese hamster ovary (CHO) cells (Cat# CCL-61, ATCC). 5 μg of each protein were loaded on 10% SDS-PAGE gels under reducing as well as non-reducing conditions. Gels were stained with 0.3% Coomassie Brilliant Blue R-250 and destained with 20% methanol.

### Western blotting and digestion of proteins with N-glycosidase F

To validate the identity of the purified protein, Western blotting analysis was performed [33]. Briefly, different amounts of the purified protein (1, 0.5, 0.25 μg) were separated by electrophoresis in 4-12% Bis-Tris protein gels, and then transferred to a polyvinylidene difluoride membrane. The membrane was probed using antibodies specific either for Fc fragment (horseradish peroxidase (HRP)-conjugated rabbit F(ab')2 anti-human IgG, Fc-fragment specific (ImmunoResearch Lab) or HRP*Polyclonal Rabbit Anti-Human

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IgG (Fc) (Cat#C030222, Cellway-Lab, Luoyang, China)), or for human VEGFR1 (Cat# 10136-RP02, Sino Biological Inc) followed by incubation with secondary antibody (HRP-conjugated Affinipure F(ab')2 Fragment Goat Anti Rabbit IgG1, F(ab')2 Fragment Specific (ImmunoResearch Lab)). Specific bands were visualized via the ECL kit according to the manufacturer's instructions (Amersham).

To analyze the impact of glycosylation on protein activity, HB-002.1 protein (Lot#20130521, 3.62 mg/ml) diluted to 0.5 mg/ml in 100 mM of ammonium bicarbonate was incubated with N-glycosidase F (Cat#11365193001, Sigma) (5 Unit/10 μg protein) at 37°C for 18 hours. Digested and non-digested proteins were analyzed in 12% SDS-PAGE under reducing and non-reducing conditions. In parallel, the digested protein was also assayed for target binding activity, which was compared to that of the parental protein.

### Target-binding assay

Target binding affinity of HB-002.1 was measured by ELISA in Falcon 96-Well ELISA Micro Plates coated overnight at room temperature with VEGF ligands or PIGF (R&D Systems) in PBS (100 ng per well). Coated plates were blocked with 3% dry fat milk in PBS-T buffer (PBS containing 0.05% Tween-20) and then 100 μl of serially diluted HB-002.1 or bevacizumab (Lot#:N3526, Roche) or hIgG-Fc (Cat#:10702-HNAH, Sino Biological Inc) (from 5 nM to 0.0024 nM) were transferred into the plates. After incubation at room temperature for 1 hour, plates were washed 5 times with PBS-T solution, and then incubated with HRP-conjugated Fc-specific antibody (Cat#C030222, Cellway-Lab, Luoyang, China) at room temperature for 1 hour. Plates were washed 5 times with PBS-T buffer and then developed with 100 μl of HRP-substrate solution for up to 5 minutes. The reaction was stopped with 1 N $H_2SO_4$, and the absorbance at 450 nM was determined in a standard plate reader.

To determine the kinetic target binding affinity of HB-002.1, varying amounts of VEGF-A were mixed with 0.5 nM of HB-002.1, Flt1[2]-Fc, hIgG-Fc or bevacizumab and then incubated for 2 hours at room temperature. The mixtures were transferred to VEGF-A coated plates and incubated for 1 hour at room temperature, the non-bound proteins in solution were washed away, and the amounts of HB-002.1, Flt1[2]-Fc, hIgG-Fc or bevacizumab bound to the plates were measured by HRP-conjugated rabbit anti-human IgG-Fc antibody. The kinetic binding affinities were analyzed according to the amounts of free VEGF blocker in the mixtures.

### VEGFR2 phosphorylation assay

4 ml of human umbilical vein endothelial cells (HUVECs) (Cat#HUVEC-004, ALLCELLS) in complete HUVEC-adapted medium (Cat#H-004, ALLCELLS) were incubated in 6 cm dishes at 37°C, 5% $CO_2$ for 24 hours, cells were starved for 2 hours and then challenged for 15 minutes with either medium alone, or VEGF-A (20 ng/ml) only, or VEGF-A pre-incubated with varying amounts of HB-002.1. Cells were washed twice with cold PBS and then dissolved in 200 μl of lysis buffer (50 mM Tris, pH 7.4, 1% sodium deoxycholate, 1% Triton X-100, 0.1% SDS, 1 mM EDTA, pH 8.0, 150 mM NaCl). After centrifugation and quantitation, equal amounts of supernatant from each sample were subjected to Western blotting analysis using antibodies specific either for total VEGFR2 (Cat# 2479, Cell Signaling Technology) or for VEGFR2 phosphotyrosine (Cat# 3770S, Cell Signaling Technology).

### VEGF-induced HUVEC proliferation and tube formation assay

HUVEC proliferation in response to VEGF-A and the impact of HB-002.1 on cell proliferation was measured using CCK-8 kits (Cat# CK04-11, DOJINDO Laboratories) following the manufacturer's instructions. Briefly, 2000 HUVECs per well were plated in a 96-well plate, which was incubated at 37°C for 2 hours. 100 μl of reagent solution containing 20 ng/ml of VEGF-A and varying amounts of HB-002.1, bevacizumab or hIgG-Fc were transferred to the plate. Cells were cultured for 72 hours at 37°C, and then CCK-8 was added to these cultures, which were incubated for 4 additional hours followed by spectrophotometric analysis at 450 nm.

The VEGF-induced tube formation assay was conducted as previously described [34]. Briefly, 50 μl of HUVECs at 3 × $10^5$/ml in culture medium were mixed with 50 μl of culture medium containing 20 ng/ml of VEGF-A plus 1000 nM HB-002.1 protein, bevacizumab or control human IgG. The mixtures were added to 96-well plates containing 50 μl of solidified Matrigel. Plates were incubated in a cell culture incubator at 37°C for 24 hours. Tube formation was observed using an inverted phase contrast microscope (Eclipse TS100, Nikon). Images were captured with a CCD color camera (KP-D20AU, Hitachi) attached to the microscope using 40x magnification plus 1.5x amplification by the CCD camera. The tube length in three different fields was measured using Image-Pro Plus software (Version 6.0, Media Cybernetics).

### Angiogenesis analysis

The impact of HB-002.1 on angiogenesis was investigated using a transgenic zebrafish embryonic angiogenesis model [35]. Briefly, the tested protein or control drugs were microinjected into the common cardinal vein of zebrafish at 48 hours post-fertilization (hpf). The subintestinal vessels (SIVs) were visualized under a Multi-Purpose Zoom Microscope (Nikon AZ100), and the area of the SIVs at 72 hpf was measured as mean fluoresence intensity (MFI) using NIS-Elements D imaging software. The percentage of angiogenesis inhibition was calculated as (MFI of vehicle

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treated SIVs - MFI of drug treated SIVs)/MFI of vehicle treated SIVs x 100.

### Pharmacokinetic analysis

16 BALB/c mice (female, age of 4-5 weeks, body weight of 18-20 g) received a subcutaneous (s.c.) injection of 50 μg HB-002.1 protein (~2.5 mg/kg mouse) and bled at 1, 2, 4, 6, 24, 48, 72, and 144 hours after injection. Levels of HB-002.1 in the plasma were measured by ELISA assay using human VEGF165 (R&D Systems) as capture protein and HRP-anti-human Fc (Jackson ImmunoResearch Lab) as the detection antibody.

### *In vivo* efficacy study

Mouse xenograft tumor models using human Colo-205 and A549 cancer cells were applied to the investigation of the *in vivo* efficacy of HB-002.1. Cells purchased from ATCC were resuspended in serum-free medium. BALB/c nude mice were ordered from Shanghai SLAC Laboratory Animal Co. Ltd. The animals were specific pathogen free and approximately 4 - 5 weeks old upon arrival at PharmaLegacy Laboratories. The procedures that were applied to animals in this protocol had been approved by PharmaLegacy Laboratories IACUC before the execution of the study. Approximately $5 \times 10^6$ cells in 200 μl of serum-free medium/matrigel (50:50 v/v) were injected s.c. in the right flank of each of the 70 mice for each model under anesthesia by 3 - 4% isoflurane. When the average tumor volume reached 100 - 200 $mm^3$, 50 mice bearing tumors of suitable size were randomized into 5 groups (10 mice per group) according to tumor volume and body weight. Mice were treated with two different doses (5 mg/kg, 20 mg/kg) of HB-002.1 or control drugs by intraperitoneal (i.p.) injections twice weekly for four weeks except for doxorubicin which was given only in one injection. Tumor volume and body weight were measured twice a week until the termination of the study. Tumor growth inhibition (TGI%) = (1-(change in mean treated tumor volume/change in mean control untreated tumor volume)) × 100. Tumor weight measured at time of mice sacrifice.

### Histology analysis

Tumors were harvested and sectioned at the end of the experiments. Tumor sections were subsequently dewaxed and rehydrated. After quenching endogenous peroxidase activity, sections were immunohistochemically stained with respective antibody. Stained sections were dehydrated in alcohol and xylene, and then mounted. The procedure for hematoxylin and eosin (H&E) staining of tumor sections was as follows: dewaxing in xylene, gradient ethanol dehydration, hematoxylin staining, rinsing with tap water, counterstaining with eosin, rinsing with ethanol, gradient ethanol dehydration, and vitrification with xylene. Immunohistochemical staining was performed using antibodies specific for CD31 (Cat#: ab9498, Abcam) followed by goat anti-mouse secondary antibody (Cat#: KIT5002, Fuzhou Maixim) and goat anti-rabbit secondary antibody (Cat#: KIT5005, Fuzhou Maixim), respectively. The microvessel density was quantified by the visual approximation technique, which involved manual counting vessels in three different microscope fields at 10x magnification. The histology results were analyzed by a pathologist on a single-blind basis. For tumor necrosis evaluation on H&E stained slides, homogenous staining in pink or pale color without cellular profiles/outline were considered necrotic cells, while cellular profiles/outlines with dark blue nuclei were considered healthy cells.

### Statistics

Statistical software used for data analysis and presentation was SAS 9.3 (SAS Institute), Prism 5 (GraphPad Software), and Excel 11 (Microsoft). Binding curves were calculated and presented using Prism 5 nonlinear regression least squares fit sigmoidal dose-response variable slope (also known as four-parameter dose-response) curves. Comparisons between different treatment groups in HUVEC proliferation was performed using a two-way analysis of variance (ANOVA), which included the main effects of treatment group and log10 concentration, as well as the treatment group x log10 concentration interaction. Upon finding a significant interaction effect, separate one-way ANOVA comparisons were carried out at each concentration. If a significant difference was found, then Tukey's multiple comparisons were used. Comparisons between different treatment groups in tube formation by one-way ANOVA provided a F-test with a small P value ($P = 0.0015$) supporting subsequent Tukey's multiple comparison test. Comparisons between control (vehicle-treated) and different treatment groups for inhibition of zebrafish angiogenesis were made by Dunnett's multiple comparison test. *In vivo* tumor volumes and weights were expressed as mean ± standard error of the mean or geometric mean with 95% confidence interval. Comparisons between different *in vivo* treatments and control PBS treated mice for changes in tumor weights were made by Mann-Whitney two-tailed test. For tumor volume, repeated measures (RM) ANOVA with a mixed models approach was used to determine if the treatment groups behaved differently across time (i.e. the "group x time" interaction). A $\log_{10}$ transformation of tumor volume was used to satisfy the required underlying assumptions of this statistical model. Since graphical analysis and theoretical considerations suggest that tumor volume grows logarithmically, such that its rate of growth decreases over time, a $\log_{10}$transformation was applied to day (specifically, $\log_{10}$of Day +1), and included as a linear main effect, as well as in the interaction term with group. The model contained one repeated "within subjects" factor of time, a "between

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animals" factor of treatment group, and the group x time interaction. Both group and time were considered fixed effects in each of the RM ANOVA models, as necessarily was, the group x time interaction. Upon finding a significant difference, interest only focused on the comparison of the treatment groups to control (PBS), but not amongst each other. To calculate the statistical significance of treatments on TGI%, we calculated the ratio of tumor volume at Day 35 relative to Day 0 for each mouse, followed by a log transformation of this ratio to achieve normality (log Day35/Day0), which is analytically equivalent to looking at percent change in tumor volume, but is more suited to conventional analysis. ANOVA was then used to compare the mean log ratios with the Student-Newman-Keuls test to make multiple comparisons. $P < 0.05$ was considered significant. For CD31 staining of tumor sections, only group descriptive statistics were calculated. No inferential statistical comparisons were performed since the sample size was so small ($n = 3$).

## Results

### Engineering and production of HB-002.1

It has been documented that the second Ig-like domain (D2) of human VEGFR1 (Flt1[2]) is critical to VEGF binding [32], however the purified Flt1[2] fused with Fc did not bind to VEGF at all, and neither did truncated protein containing the first 2 domains (Flt1[1,2]) or that containing domains 2 and 3 (Flt1[2,3]) [32]. Only protein containing domains 1-3 had full VEGF binding activity comparable to that of the whole extracellular portion of wild type VEGFR1. This phenomenon was confirmed as well by Barleon et al [36], revealing the requirement of VEGF binding for the first three Ig-like domains. Based on these studies, we designed the HB-002.1 protein in which 5 flanking amino acids (S129-R133) at the N-terminal and 2 amino acids (N227, T228) at the C-terminal of the D2 domain were included with D2 (Figure 1A). The D2 domain-only (Flt1[2]-Fc) was also expressed as a control for VEGF binding assay.

The HB-002.1 and Flt1[2]-Fc proteins were produced in CHO cells upon transfection with the corresponding construct. The secreted proteins were purified and resolved in 10% SDS-PAGE gels showing MWs of HB-002.1 and Flt1[2]-Fc at ~110 kDa in non-reducing conditions, and ~45 kDa in reducing conditions (Figure 1B), both relatively larger than the calculated MW, which is most likely due to glycosylation since there are two N-linked glycosylation sites in the D2 domain. Bevacizumab resolved in the correct MW positions (Figure 1B).

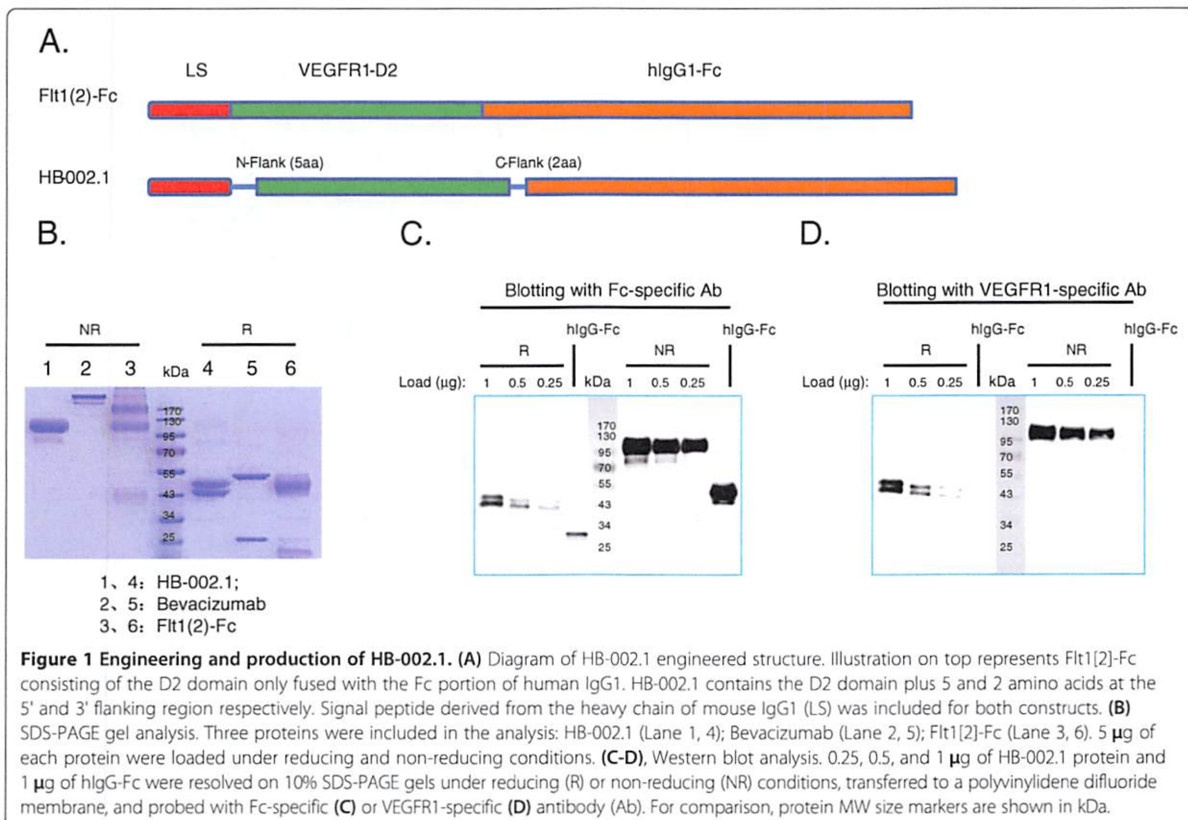


**Figure 1 Engineering and production of HB-002.1. (A)** Diagram of HB-002.1 engineered structure. Illustration on top represents Flt1[2]-Fc consisting of the D2 domain only fused with the Fc portion of human IgG1. HB-002.1 contains the D2 domain plus 5 and 2 amino acids at the 5' and 3' flanking region respectively. Signal peptide derived from the heavy chain of mouse IgG1 (LS) was included for both constructs. **(B)** SDS-PAGE gel analysis. Three proteins were included in the analysis: HB-002.1 (Lane 1, 4); Bevacizumab (Lane 2, 5); Flt1[2]-Fc (Lane 3, 6). 5 μg of each protein were loaded under reducing and non-reducing conditions. **(C-D)**, Western blot analysis. 0.25, 0.5, and 1 μg of HB-002.1 protein and 1 μg of hIgG-Fc were resolved on 10% SDS-PAGE gels under reducing (R) or non-reducing (NR) conditions, transferred to a polyvinylidene difluoride membrane, and probed with Fc-specific **(C)** or VEGFR1-specific **(D)** antibody (Ab). For comparison, protein MW size markers are shown in kDa.

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