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(54) Titre : COMPOSITIONS COMPRENANT UN ARN^{si} DE EGFR HUMAIN ET LEURS PROCEDES D'UTILISATION
(54) Title: COMPOSITIONS COMPRISING HUMAN EGFR-siRNA AND METHODS OF USE

(57) **Abrégé/Abstract:**

The present invention provides nucleic acid molecules that inhibit EGFR expression. Methods of using the nucleic acid molecules are also provided.



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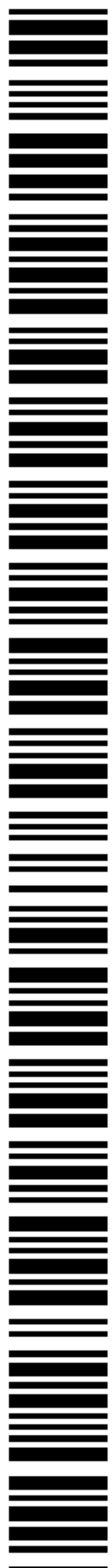
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COMPOSITIONS COMPRISING HUMAN EGFR-siRNA AND METHODS OF USE

Cross-reference to related applications

5 [0001] This application claims priority under 35 U.S.C. § 119(e) from United States provisional application 60/945,842, filed June 22, 2007, United States provisional application 60/998,284, filed October 10, 2007, United States provisional application 61/124,223, filed April 14, 2008 and United States provisional application 61/060,721, filed June 11, 2008.

Field of the Invention

10 [0002] The present invention is in the field of molecular biology and medicine and relates to short interfering RNA (siRNA) molecules for modulating the expression of Epidermal Growth Factor (EGF) receptor.

Background of the Invention

15 [0003] EGFR, is a 170 kDa transmembrane glycoprotein that has been shown to play an important role in controlling cell proliferation and differentiation. EGFR is a member of the ErbB family of receptors, that includes EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). EGFR is composed of extracellular, transmembrane and cytoplasmic domains. Ligand binding to the extacellular domain of EGFR leads to dimerization and activation of a tyrosine
20 kinase activity, initiating a complex cascade of enzymatic and biological events leading to cell proliferation and differentiation.

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5 [0004] Overexpression of EGFR has been associated with many malignancies, including ones of the lung, kidney, pancreas, breast, head and neck, stomach and colon. Various cells have been shown to produce variant form(s) of EGFR. A431 human epidermoid carcinoma cells, for example, have been shown to produce a truncated EGFR.

[0005] The role of EGFR in cancer has been validated by the recent FDA approval of several EGFR inhibitors including neutralizing antibodies such as Vectibix and Erbitux and small molecule TKi such as Tarceva™ for the treatment of metastatic colon, lung, pancreas, and head and neck cancers.

10 [0006] RNA interference (RNAi) technology is emerging as an effective means for reducing the expression of specific gene products and may therefore prove to be uniquely useful in a number of therapeutic, diagnostic, and research applications for the modulation of expression of EGFR. The present invention provides compositions and methods for modulating expression of these proteins using RNAi
15 technology.

[0007] Thus, there is a need in the art for compositions and methods for modulating the expression of EGFR as a therapeutic approach for the treatment of cancer and other diseases. The present invention provides this and other advantages.

20 Summary of the Invention

[0008] One aspect of the present invention provides a nucleic acid molecule that down regulates expression of an epidermal growth factor (EGF) receptor gene, wherein the nucleic acid molecule comprises a nucleotide sequence that targets EGFR mRNA, wherein the nucleic acid molecule comprises a nucleotide sequence
25 that targets any one of the polynucleotide sequences set forth in SEQ ID NOs: 1-10 or 21-121. In a particular embodiment, the nucleic acid is an siRNA molecule. In more particular embodiments, the siRNA comprises any one of the single stranded RNA sequences provided in SEQ ID NOs: 11-20 and 122-323, or a double-stranded RNA thereof. In certain embodiments, the nucleic acid molecule down
30 regulates expression of an EGFR gene via RNA interference (RNAi).

[0009] In another embodiment, the present invention provides for a composition comprising any one or more of the siRNA molecules, wherein the siRNA

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comprises any one of the single stranded RNA sequences provided in SEQ ID NOs: 11-20 and 122-323, or a double-stranded RNA thereof. In this regard, the composition may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more siRNA molecules of the invention. In particular
5 embodiments, the siRNA comprises a targeting moiety.

[0010] In various embodiments, the present invention provides a method for treating or preventing a cancer in a subject with an EGFR expressing cancer and having or suspected of being at risk for having the cancer, comprising
10 administering to a subject a composition comprising any one of the single stranded RNA sequences provided in SEQ ID NOs: 11-20 and 122-323, or a double-stranded RNA thereof, thereby treating or preventing the cancer. In certain embodiments, the cancer is selected from the group consisting of breast cancer, lung cancer, prostate cancer, colorectal cancer, brain cancer, esophageal cancer,
15 stomach cancer, bladder cancer, pancreatic cancer, cervical cancer, head and neck cancer, kidney cancer, endometrial cancer, ovarian cancer, meningioma, melanoma, lymphoma, and glioblastoma.

[0011] In another embodiment, the present invention provides a method for inhibiting the synthesis or expression of EGFR comprising contacting a cell
20 expressing EGFR with one or more siRNAs, wherein the siRNAs comprise a sequence as set forth in SEQ ID NOs: 11-20 or 122-323.

[0012] These and other aspects of the present invention will become apparent upon references to the following detailed description.

Brief Description of the Drawing(s)

25 [0013] Figure 1 is a bar graph depicting *in vitro* inhibition of hEGFR by certain siRNA molecules.

[0014] Human EGFR gene silencing activity of human EGFR-siRNA was tested in HT-29 cells. The HT-29 cells were transfected with the EGFR-siRNAs using an Electroporation mediated transfection method with 4 or 8 ug siRNA per 2x10⁶
30 cells/200 ul. The concentration of EGFR protein in the transfected HT-29 cells was measured at 72 hours post transfection using a hEGFR ELISA kit (R&D Systems, Inc.). The concentration of hEGFR protein was normalized against total cellular

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protein and the percentage of hEGFR inhibition was normalized against cells treated with a mock process without siRNA. All 5 hEGFR siRNA demonstrated inhibition of hEGFR production. The hEGFR-25-1 and hEGFR-25-2 were the most potent siRNA with a more than 70% inhibition of hEGFR protein at 72 hours post siRNA transfection.

[0015] Figure 2 is a bar graph demonstrating the inhibition of hEGFR by two siRNA molecules in a dose-dependent manner.

[0016] The selected hEGFR-siRNA, hEGFR-25-1 and hEGFR-25-2, were tested for their capability of inhibiting hEGFR expression in a dose-dependent manner.

10 The HT-29 cells were transfected with the EGFR-siRNAs in a range of 0.01 -10 ug siRNA per 2×10^6 cells/200 μ l using an electroporation mediated transfection method. The concentration of EGFR protein in the transfected HT-29 cells was measured at 48 hours post transfection using a hEGFR ELISA kit (R&D Systems, Inc.). The concentration of hEGFR protein was normalized against total cellular protein and the percentage of hEGFR inhibition was normalized against cells treated with a mock process without siRNA. Both hEGFR-25-1 and hEGFR-25-2 demonstrated a dose-dependent inhibition of hEGFR production.

[0017] Figure 3 is a line graph demonstrating the tumor inhibition effect of hEGFR-siRNA-PolyTran™ NPX on A431 tumor xenografts.

20 [0018] Antitumor efficacy of PolyTran™ (PT-NPX) carrying hEGFR-siRNA was determined in A431 (epidermoid carcinoma) xenograft model. Mice bearing established A431 tumors were treated with intravenous administration of PolyTran NPX carrying hEGFR-siRNA every other day for 6 times started on Day 4 post tumor cells implantation. Treatment controls included no treatment (untreated) and Erlotinib (Tarceva™) which was daily administered orally at 100 mg/kg for 6 days. Treatment with PT-NPX carrying human EGFR siRNA significantly inhibited A431 tumor growth in comparison with untreated control; and the inhibition effect was more profound than the Tarceva™ treatment control.

25 [0019] Figure 4 is a line graph demonstrating the inhibition of A431 tumor growth by PT-EGFR-siRNA NPX is hEGFR-siRNA specific and requires formulation of PT-siRNA NPX.

- [0020] PolyTran™ nanoparticles (PT-NPX) carrying hEGFR-siRNA or negative control-siRNA, as well as the PolyTran peptide alone or hEGFR-siRNA alone, were tested in A431 (epidermoid carcinoma) xenograft model. Mice bearing established A431 tumors were treated with intravenous administration of PolyTran NPX carrying hEGFR-siRNA or negative control-siRNA (2 mg/kg), or hEGFR-siRNA alone, or PolyTran peptide alone every other day for 4 times started on Day 5 post tumor cells implantation. Treatment controls included no treatment (untreated). Only the treatment with PT-NPX carrying human EGFR siRNA significantly inhibited A431 tumor growth in comparison with untreated control. All other treatment groups include PT-NPX carrying control-siRNA, hEGFR-siRNA alone, or PolyTran peptide, did not inhibit A431 tumor growth.
- [0021] Figure 5 is a line graph demonstrating the tumor inhibition effect of hEGFR-siRNA-PolyTran™ NPX on A549 tumor xenografts.
- [0022] The antitumor efficacy of PolyTran™ (PT-NPX) carrying hEGFR-siRNA was determined in A549 (NSCLC) xenograft model. Mice bearing established A549 tumors were treated with intravenous administration of PolyTran NPX carrying hEGFR-siRNA every other day for 6 times started on Day 9 post tumor cells implantation. Treatment controls included no treatment (untreated) and Erlotinib (Tarceva™) which was daily administered orally at 100 mg/kg for 6 days. Treatment with PT-NPX carrying human EGFR siRNA significantly inhibited A549 tumor growth in comparison with untreated control; and the inhibition effect was more profound than the Tarceva™ treatment control. The PT-NPX carrying control-siRNA did not have inhibition effect on A549 tumor growth.
- [0023] Figure 6 is a schematic showing the structure and composition of the PolyTran™. PolyTran™ is a synthetic biodegradable cationic branched polypeptide. The positively charged PolyTran™ polypeptide serves as a carrier and condenser for the negatively charged siRNA.
- [0024] Figure 7 is a diagram showing the histidine-lysine H3K4b polypeptide structure. The histidine-lysine H3K4b polypeptide was used in the formulation of PT-NPX.

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[0025] Figure 8 is an electronic image of PolyTran-siRNA NPX. When PolyTran polypeptide was mixed with siRNA (against hVEGF), spherical shaped nanoparticles (PT-siRNA NPX) with diameter around 100 nm were formed in solution.

5 [0026] Figure 9 shows fluorescent microscope images demonstrating cellular uptake of PT-siRNA NPX. Mouse endothelial EA.hy926 cells were transfected with the PT-NPX containing Alexa488-labeled hVEGF siRNA (QIAGEN) at equivalent siRNA concentration of 5 ug/mL for 6 hours. The fluorescence observed within the cells suggest internalization of the PT-siRNA NPX.

10 [0027] Figure 10 shows fluorescent microscope images demonstrating tissue distribution of PT-siRNA NPX in tumors. Biodistribution of the PT-NPX following i.v. injection was investigated using the PT NPX carrying fluorescently labeled siRNA (Alexa-555 labeled hVEGF siRNA from QIAGEN). Nude mice bearing A431 xenografts were injected intravenously. with the PT-NPX. One hour post injection, the tumor tissues were removed and frozen tissue sections were prepared.

15 Fluorescence labeled siRNA was found in the tumor tissue, indicating distribution of the PT-NPX in tumor tissue was achieved. No auto- fluorescent background is seen in the untreated tumor tissues.

[0028] Figures 11A-C are line graphs demonstrating hVEGF gene silencing by VEGF siRNA. Target gene silencing activity of human VEGF-siRNA was tested in

20 human prostate cancer PC-3 cells. The cells were transfected with the siRNA using LipoFectamine RNAiMax (Invitrogen). The concentration of VEGF in the media were measured at 24 (Fig. 11A), 48 (Fig. 11B) and 72 (Fig. 11C) hours post transfection using an ELISA kit (R&D Systems, Inc.). All three human VEGF siRNA tested inhibited the production of VEGF in a dose-dependent manner and have nano-

25 or subnano-molar potency.

[0029] Figure 12 is a bar graph demonstrating hVEGF gene silencing by PT-siRNA NPX. The human prostate cancer cell line PC-3, which expresses VEGF, was treated with PT-NPX carrying hVEGF-siRNA or Control siRNA in serum-free medium for 4 hours, and then replenished with serum (10%). 72 hours after the treatment, cell

30 lysates were collected for the measurement of VEGF using an ELISA kit (R&D Systems, Inc.). PT-NPX containing hVEGF siRNA suppressed hVEGF production *in vitro*.

[0030] Figure 13 is a line graph showing the effect of PT-siRNA NPX on human epidermoid carcinoma A431 tumor volume. Human epidermoid carcinoma A431 cells

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were implanted subcutaneously in female nude mice. PT-NPX with equivalent siRNA of 2 mg/kg was injected intravenously when tumor volume reached 80-100 mm³. Injection schedules are indicated by the arrows below the transverse axis. Treatment with PT-NPX containing human VEGF-siRNA or mouse VEGFR2-siRNA (sense strand: 5'-ggaaggcccauugaguccaacuaca-3' (SEQ ID NO: 327) and antisense strand: 5'-uguaguuggacucaaugggccuucc-3' (SEQ ID NO: 328)) significantly inhibited tumor growth in comparison with untreated or GFP-siRNA NPX treated controls. The antitumor efficacy was comparable to that of Avastin at 5 mg/kg via i.p. injection. No obvious body weight loss or clinical abnormality in any of the hVEGF-siRNA or mVEGFR2 PT-NPX treated animals was observed.

[0031] Figure 14 is a bar graph showing *in vivo* knockdown of mouse VEGFR2 mRNA in A549 tumors through systemic treatment with PT-mVEGFR2-siRNA NPX. The *in vivo* target gene knockdown by PT-siRNA NPX was examined in the A549 xenograft model. Upon establishment of the xenograft tumors, the mice (n=6) were treated i.v. with PT-NPX carrying mVEGFR2-siRNA (sense strand: 5'-ggaaggcccauugaguccaacuaca-3' (SEQ ID NO: 327) and antisense strand: 5'-uguaguuggacucaaugggccuucc-3' (SEQ ID NO: 328)) or Control-siRNA at 2 mg/kg daily for 3 days. At 24 hours after the last injection, the tumors were removed, and total RNA from tumor tissues were isolated and subjected to a relative quantitative real-time PCR assay. Treatment with PT-mVEGFR2-siRNA NPX resulted in a significant knockdown (between 30-90% in repeated experiments) of mVEGFR2 mRNA in A549 xenografts.

Detailed Description of the Invention

[0032] The present invention relates to nucleic acid molecules for modulating the expression of EGFR. In certain embodiments the nucleic acid is ribonucleic acid (RNA). In certain embodiments, the RNA molecules are single or double stranded. In this regard, the nucleic acid based molecules of the present invention, such as siRNA, inhibit or down-regulate expression of EGFR.

[0033] The present invention relates to compounds, compositions, and methods for the study, diagnosis, and treatment of traits, diseases and conditions that respond to the modulation of EGFR gene expression and/or activity. The present invention is also directed to compounds, compositions, and methods relating to

traits, diseases and conditions that respond to the modulation of expression and/or activity of genes involved in EGFR gene expression pathways or other cellular processes that mediate the maintenance or development of such traits, diseases and conditions. Specifically, the invention relates to double stranded nucleic acid molecules including small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules capable of mediating RNA interference (RNAi) against EGFR gene expression, including cocktails of such small nucleic acid molecules and nanoparticle formulations of such small nucleic acid molecules. The present invention also relates to small nucleic acid molecules, such as siNA, siRNA, and others that can inhibit the function of endogenous RNA molecules, such as endogenous micro-RNA (miRNA) (*e.g.*, miRNA inhibitors) or endogenous short interfering RNA (siRNA), (*e.g.*, siRNA inhibitors) or that can inhibit the function of RISC (*e.g.*, RISC inhibitors), to modulate EGFR gene expression by interfering with the regulatory function of such endogenous RNAs or proteins associated with such endogenous RNAs (*e.g.*, RISC), including cocktails of such small nucleic acid molecules and nanoparticle formulations of such small nucleic acid molecules. Such small nucleic acid molecules are useful, for example, in providing compositions to prevent, inhibit, or reduce breast, lung, prostate, colorectal, brain, esophageal, bladder, pancreatic, cervical, head and neck, and ovarian cancer, melanoma, lymphoma, glioma, multidrug resistant cancers, and any other cancerous disease and/or other disease states, conditions, or traits associated with EGFR gene expression or activity in a subject or organism.

25 [0034] By "inhibit" or "down-regulate" it is meant that the expression of the EGFR gene, or level of mRNA encoding an EGFR protein, levels of EGFR protein, or activity of EGFR is reduced below that observed in the absence of the nucleic acid molecules of the invention. In one embodiment, inhibition or down-regulation with the nucleic acid molecules of the invention is below that level observed in the presence of an inactive control or attenuated molecule that is able to bind to the same target RNA, but is unable to cleave or otherwise silence that RNA. In another embodiment, inhibition or down-regulation with the nucleic acid

molecules of the invention is preferably below that level observed in the presence of, for example, a nucleic acid with scrambled sequence or with mismatches. In another embodiment, inhibition or down-regulation of EGFR with the nucleic acid molecule of the instant invention is greater in the presence of the nucleic acid molecule than in its absence.

[0035] By "modulate" is meant that the expression of the EGFR gene, or level of mRNA encoding an EGFR protein, levels of EGFR protein, or activity of EGFR is up-regulated or down-regulated, such that the expression, level, or activity is greater than or less than that observed in the absence of the nucleic acid molecules of the invention.

[0036] By "double stranded RNA" or "dsRNA" is meant a double stranded RNA that matches a predetermined gene sequence that is capable of activating cellular enzymes that degrade the corresponding messenger RNA transcripts of the gene. These dsRNAs are referred to as short interfering RNA (siRNA) and can be used to inhibit gene expression (see for example Elbashir *et al.*, 2001, Nature, 411, 494-498; and Bass, 2001, Nature, 411, 428-429). The term "double stranded RNA" or "dsRNA" as used herein also refers to a double stranded RNA molecule capable of RNA interference "RNAi", including short interfering RNA "siRNA" (see for example Bass, 2001, Nature, 411, 428-429; Elbashir *et al.*, 2001, Nature, 411, 494-498; and Kreutzer *et al.*, International PCT Publication No. WO 00/44895; Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.*, International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO 01/29058; Deschamps-Depaillette, International PCT Publication No. WO 99/07409; and Li *et al.*, International PCT Publication No. WO 00/44914). The dsRNA may be a 25-mer. The dsRNA may be blunt-ended or comprise single-stranded overhangs.

[0037] By "gene" it is meant a nucleic acid that encodes an mRNA, for example, nucleic acid sequences include but are not limited to structural genes encoding a polypeptide.

[0038] By "a nucleic acid that targets" is meant a nucleic acid as described herein that matches, is complementary to or otherwise binds or specifically hybridizes to

and thereby modulates the expression of the gene that comprises the target sequence, or level of mRNA encoding an EGFR protein, levels of EGFR protein, or activity of EGFR.

5 [0039] "Complementarity" refers to the ability of a nucleic acid to form hydrogen bond(s) with another RNA sequence by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its target or complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, *e.g.*, enzymatic nucleic acid cleavage, antisense or triple helix inhibition. Determination of binding free energies for nucleic acid molecules is well known in the art (see, *e.g.*, Turner *et al.*, 1987, CSH Symp. Quant. Biol. LII pp. 123-133; Frier *et al.*, 1986, Proc. Nat. Acad. Sci. USA 83:9373-9377; Turner *et al.*, 1987, J. Am. Chem. Soc. 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule which
15 can form hydrogen bonds (*e.g.*, Watson-Crick base pairing) with a second nucleic acid sequence (*e.g.*, 5, 6, 7, 8, 9, 10 out of 10 being 50%, 60%, 70%, 80%, 90%, and 100% complementary). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

20 [0040] By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By "ribonucleotide" or "2'-OH" is meant a nucleotide with a hydroxyl group at the 2' position of a β -D-ribo-furanose moiety.

[0041] By "RNA interference" or "RNAi" is meant a biological process of inhibiting or down regulating gene expression in a cell as is generally known in the art and which is mediated by short interfering nucleic acid molecules (see for
25 example Zamore and Haley, 2005, Science, 309, 1519-1524; Vaughn and Martienssen, 2005, Science, 309, 1525-1526; Zamore *et al.*, 2000, Cell, 101, 25-33; Bass, 2001, Nature, 411, 428-429; Elbashir *et al.*, 2001, Nature, 411, 494-498; and Kreutzer *et al.*, International PCT Publication No. WO 00/44895; Zemicka-
30 Goetz *et al.*, International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.*, International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO

01/29058; Deschamps-Depaillette, International PCT Publication No. WO 99/07409; and Li *et al.*, International PCT Publication No. WO 00/44914; Allshire, 2002, Science, 297, 1818-1819; Volpe *et al.*, 2002, Science, 297, 1833-1837; Jenuwein, 2002, Science, 297, 2215-2218; and Hall *et al.*, 2002, Science, 297, 2232-2237; Hutvagner and Zamore, 2002, Science, 297, 2056-60; McManus *et al.*, 2002, RNA, 8, 842-850; Reinhart *et al.*, 2002, Gene & Dev., 16, 1616-1626; and Reinhart & Bartel, 2002, Science, 297, 1831). In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, transcriptional inhibition, or epigenetics. For example, siRNA molecules of the invention can be used to epigenetically silence genes at both the post-transcriptional level or prior to transcriptional initiation. In a non-limiting example, epigenetic modulation of gene expression by siRNA molecules of the invention can result from siRNA mediated modification of chromatin structure or methylation patterns to alter gene expression (see, for example, Verdel *et al.*, 2004, Science, 303, 672-676; Pal-Bhadra *et al.*, 2004, Science, 303, 669-672; Allshire, 2002, Science, 297, 1818-1819; Volpe *et al.*, 2002, Science, 297, 1833-1837; Jenuwein, 2002, Science, 297, 2215-2218; and Hall *et al.*, 2002, Science, 297, 2232-2237). In another non-limiting example, modulation of gene expression by siRNA molecules of the invention can result from siRNA mediated cleavage of RNA (either coding or non-coding RNA) via RISC, or alternately, translational inhibition as is known in the art. In another embodiment, modulation of gene expression by siRNA molecules of the invention can result from transcriptional inhibition (see for example Janowski *et al.*, 2005, Nature Chemical Biology, 1, 216-222).

[0042] In certain embodiments, the nucleic acid inhibitors comprise sequences which are complementary to any known EGFR sequence, including variants thereof that have altered expression and/or activity, particularly variants associated with disease. Variants of EGFR include sequences having 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher sequence identity to the wild type EGFR sequences, wherein such EGFR variants may demonstrate altered (increased or decreased) tyrosine kinase activity. As would be

understood by the skilled artisan, EGFR sequences are available in any of a variety of public sequence databases including GENBANK or SWISSPROT. In one embodiment, the nucleic acid inhibitors (*e.g.*, siRNA) of the invention comprise sequences complimentary to the specific EGFR target sequences provided in SEQ ID NOs: 1-10 and 21-121 (see Tables 1 and 3). Examples of such siRNA molecules also are shown in the Examples and provided in SEQ ID NOs: 11-20 and 122-323 (see Tables 2 and 4).

[0043] By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

10 [0044] By "subject" is meant an organism which is a recipient of the nucleic acid molecules of the invention. "Subject" also refers to an organism to which the nucleic acid molecules of the invention can be administered. In certain embodiments, a subject is a mammal or mammalian cells. In further embodiments, a subject is a human or human cell.

15 [0045] Nucleic acids can be synthesized using protocols known in the art as described in Caruthers *et al.*, 1992, Methods in Enzymology 211, 3 19, Thompson *et al.*, International PCT Publication No. WO 99/54459, Wincott *et al.*, 1995, Nucleic Acids Res. 23, 2677-2684, Wincott *et al.*, 1997, Methods Mol. Bio., 74, 59, Brennan *et al.*, 1998, Biotechnol Bioeng., 61, 33-45, and Brennan, U.S. Pat. No. 20 6,001,311. The synthesis of nucleic acids makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μ M scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 25 second coupling step for 2'-deoxy nucleotides. Alternatively, syntheses at the 0.2 μ M scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, Calif.) with minimal modification to the cycle. A 33-fold excess (60 μ L of 0.11 M=6.6 μ M) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60 μ L of 0.25 M=15 μ M) can be used in each 30 coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40 μ L of 0.11 M=4.4 μ M) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40 μ L of 0.25 M=10 μ M) can be used in each coupling

cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by calorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include; detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% N-methylimidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM I₂, 49 mM pyridine, 9% water in THF. Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

[0046] By "nucleotide" is meant a heterocyclic nitrogenous base in N-glycosidic linkage with a phosphorylated sugar. Nucleotides are recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra*). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, Nucleic Acids Res. 22, 2183. Exemplary chemically modified and other natural nucleic acid bases that can be introduced into nucleic acids include, for example, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2,4,6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*, ribothymidine), 5-halouridine (*e.g.*, 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (*e.g.* 6-methyluridine), propyne, quesosine, 2-thiouridine, 4-thiouridine, wybutosine,

wybutoxosine, 4-acetyltidine, 5-(carboxyhydroxymethyl)uridine, 5'-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluridine, beta-D-galactosylqueosine, 1-methyladenosine, 1-methylinosine, 2,2-dimethylguanosine, 3-methylcytidine, 2-methyladenosine, 2-methylguanosine, N6-methyladenosine, 7-methylguanosine, 5-methoxyaminomethyl-2-thiouridine, 5-methylaminomethyluridine, 5-methylcarbonylmethyluridine, 5-methoxyuridine, 5-methyl-2-thiouridine, 2-methylthio-N6-isopentenyladenosine, beta-D-mannosylqueosine, uridine-5-oxyacetic acid, 2-thiocytidine, threonine derivatives and others (Burgin *et al.*, 1996, Biochemistry, 35, 14090; Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents; such bases can be used at any position, for example, within the catalytic core of an enzymatic nucleic acid molecule and/or in the substrate-binding regions of the nucleic acid molecule.

15 [0047] By "nucleoside" is meant a heterocyclic nitrogenous base in N-glycosidic linkage with a sugar. Nucleosides are recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleoside sugar moiety. Nucleosides generally comprise a base and sugar group. The nucleosides can be unmodified or modified

20 at the sugar, and/or base moiety, (also referred to interchangeably as nucleoside analogs, modified nucleosides, non-natural nucleosides, non-standard nucleosides and other; see for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman). There are several examples

25 of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, Nucleic Acids Res. 22, 2183. Exemplary chemically modified and other natural nucleic acid bases that can be introduced into nucleic acids include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2,4,6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*, ribothymidine), 5-halouridine (*e.g.*, 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (*e.g.*, 6-methyluridine), propyne, queosine, 2-thiouridine, 4-thiouridine, wybutosine,

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wybutoxosine, 4-acetylcytidine, 5-(carboxyhydroxymethyl)uridine, 5'-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluridine, beta-D-galactosylqueosine, 1-methyladenosine, 1-methylinosine, 2,2-dimethylguanosine, 3-methylcytidine, 2-methyladenosine, 2-methylguanosine, N6-methyladenosine, 7-methylguanosine, 5-methoxyaminomethyl-2-thiouridine, 5-methylaminomethyluridine, 5-methylcarbonylmethyluridine, 5-methoxyuridine, 5-methyl-2-thiouridine, 2-methylthio-N6-isopentenyladenosine, beta-D-mannosylqueosine, uridine-5-oxyacetic acid, 2-thiocytidine, threonine derivatives and others (Burgin *et al.*, 1996, Biochemistry, 35, 14090; Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleoside bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents; such bases can be used at any position, for example, within the catalytic core of an enzymatic nucleic acid molecule and/or in the substrate-binding regions of the nucleic acid molecule.

15 [0048] In certain embodiments, the nucleic acid molecules of the instant invention can be expressed within cells from eukaryotic promoters (*e.g.*, Izant and Weintraub, 1985, Science, 229, 345; McGarry and Lindquist, 1986, Proc. Natl. Acad. Sci., USA 83, 399; Scanlon *et al.*, 1991, Proc. Natl. Acad. Sci. USA, 88, 10591-5; Kashani-Sabet *et al.*, 1992, Antisense Res. Dev., 2, 3-15; Dropulic *et al.*, 20 1992, J. Virol., 66, 1432-41; Weerasinghe *et al.*, 1991, J. Virol., 65, 5531-4; Ojwang *et al.*, 1992, Proc. Natl. Acad. Sci. USA, 89, 10802-6; Chen *et al.*, 1992, Nucleic Acids Res., 20, 4581-9; Sarver *et al.*, 1990 Science, 247, 1222-1225; Thompson *et al.*, 1995, Nucleic Acids Res., 23, 2259; Good *et al.*, 1997, Gene Therapy, 4, 45). Those skilled in the art will realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by an enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 94/02595; Ohkawa *et al.*, 1992, Nucleic Acids Symp. Ser., 27, 15-16; Taira *et al.*, 1991, Nucleic Acids Res., 19, 5125-30; Ventura *et al.*, 1993, Nucleic 30 Acids Res., 21, 3249-55; Chowrira *et al.*, 1994, J. Biol. Chem., 269, 25856).

[0049] In another aspect of the invention, nucleic acid molecules of the present invention, such as RNA molecules, are expressed from transcription units (see for

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example Couture *et al.*, 1996, TIG., 12, 510) inserted into DNA or RNA vectors. The recombinant vectors are preferably DNA plasmids or viral vectors. RNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. Preferably, the recombinant
5 vectors capable of expressing the nucleic acid molecules are delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the nucleic acid molecule binds to the target mRNA. Delivery of nucleic acid molecule expressing vectors
10 can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient or subject followed by reintroduction into the patient or subject, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.*, 1996, TIG., 12, 510).

15 **[0050]** In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the nucleic acid molecules of the instant invention is disclosed. The nucleic acid sequence encoding the nucleic acid molecule of the instant invention is operably linked in a manner which allows expression of that nucleic acid molecule.

20 **[0051]** In another aspect the invention features an expression vector comprising:
a) a transcription initiation region (*e.g.*, eukaryotic pol I, II or III initiation region);
b) a transcription termination region (*e.g.*, eukaryotic pol I, II or III termination region); c) a nucleic acid sequence encoding at least one of the nucleic acid catalyst of the instant invention; and wherein said sequence is operably linked to
25 said initiation region and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the nucleic acid catalyst of the invention; and/or an intron (intervening sequences).

30 **[0052]** Transcription of the nucleic acid molecule sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are

expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, Proc. Natl. Acad. Sci. USA, 87, 6743-7; Gao and Huang 1993, Nucleic Acids Res., 21, 2867-72; Lieber *et al.*, 1993, Methods Enzymol., 217, 47-66; Zhou *et al.*, 1990, Mol. Cell. Biol., 10, 4529-37). Several investigators have demonstrated that nucleic acid molecules, such as ribozymes expressed from such promoters can function in mammalian cells (e.g., Kashani-Sabet *et al.*, 1992, Antisense Res. Dev., 2, 3-15; Ojwang *et al.*, 1992, Proc. Natl. Acad. Sci. USA, 89, 10802-6; Chen *et al.*, 1992, Nucleic Acids Res., 20, 4581-9; Yu *et al.*, 1993, Proc. Natl. Acad. Sci. USA, 90, 6340-4; L'Huillier *et al.*, 1992, EMBO J., 11, 4411-8; Lisziewicz *et al.*, 1993, Proc. Natl. Acad. Sci. U.S.A., 90, 8000-4; Thompson *et al.*, 1995, Nucleic Acids Res., 23, 2259; Sullenger & Cech, 1993, Science, 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as ribozymes in cells (Thompson *et al.*, *supra*; Couture and Stinchcomb, 1996, *supra*; Noonberg *et al.*, 1994, Nucleic Acid Res., 22, 2830; Noonberg *et al.*, U.S. Pat. No. 5,624,803; Good *et al.*, 1997, Gene Ther., 4, 45; Beigelman *et al.*, International PCT Publication No. WO 96/18736. The above ribozyme transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, 1996, *supra*).

[0053] In another aspect, the invention features an expression vector comprising nucleic acid sequence encoding at least one of the nucleic acid molecules of the invention, in a manner which allows expression of that nucleic acid molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; c) a nucleic acid sequence encoding at least one said nucleic acid molecule; and wherein said sequence is operably

linked to said initiation region and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.

- [0054] In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; d) a nucleic acid sequence encoding at least one said nucleic acid molecule, wherein said sequence is operably linked to the 3'-end of said open reading frame; and wherein said sequence is operably linked to said initiation region, said open reading frame and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. In yet another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) a nucleic acid sequence encoding at least one said nucleic acid molecule; and wherein said sequence is operably linked to said initiation region, said intron and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.
- [0055] In yet another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; e) a nucleic acid sequence encoding at least one said nucleic acid molecule, wherein said sequence is operably linked to the 3'-end of said open reading frame; and wherein said sequence is operably linked to said initiation region, said intron, said open reading frame and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.

Methods of Use and Administration of Nucleic Acid Molecules

- [0056] Methods for the delivery of nucleic acid molecules are described in Akhtar *et al.*, 1992, Trends Cell Bio., 2, 139; and Delivery Strategies for Antisense Oligonucleotide Therapeutics, ed. Akhtar; Sullivan *et al.*, PCT WO 94/02595, further describes the general methods for delivery of enzymatic RNA molecules. These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. Alternatively, the nucleic acid/vehicle combination is

locally delivered by direct injection or by use of an infusion pump. For example, the nucleic acids and compositions of the invention may be administered directly into a tumor. Other routes of delivery include, but are not limited to oral (tablet or pill form) and/or intrathecal delivery (Gold, 1997, Neuroscience, 76, 1153-1158).

5 Other approaches include the use of various transport and carrier systems, for example, through the use of conjugates and biodegradable polymers. For a comprehensive review on drug delivery strategies including CNS delivery, see Ho *et al.*, 1999, Curr. Opin. Mol. Ther., 1, 336-343 and Jain, Drug Delivery Systems: Technologies and Commercial Opportunities, Decision Resources, 1998 and
10 Groothuis *et al.*, 1997, J. NeuroVirol., 3, 387-400. More detailed descriptions of nucleic acid delivery and administration are provided in Sullivan *et al.*, *supra*, Draper *et al.*, PCT WO93/23569, Beigelman *et al.*, PCT WO99/05094, and Klimuk *et al.*, PCT WO99/04819.

[0057] The molecules of the instant invention can be used as pharmaceutical
15 agents. Pharmaceutical agents prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state in a subject.

[0058] The negatively charged polynucleotides of the invention can be administered and introduced into a subject by any standard means, with or without
20 stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as tablets, capsules or elixirs for oral administration; suppositories for rectal administration; sterile solutions; suspensions for injectable
25 administration; and the other compositions known in the art.

[0059] The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

30 [0060] A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or subject, preferably a human. Suitable forms, in part, depend upon the

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use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell. For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations
5 such as toxicity and forms which prevent the composition or formulation from exerting its effect.

[0061] By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes which lead to systemic absorption include,
10 without limitations: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes exposes the desired negatively charged nucleic acids, to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the
15 compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation which can facilitate the association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking
20 advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as cancer cells.

[0062] By pharmaceutically acceptable formulation is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired
25 activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: PEG conjugated nucleic acids, phospholipid conjugated nucleic acids, nucleic acids containing lipophilic moieties, phosphorothioates, P-glycoprotein inhibitors (such as Pluronic P85) which can enhance entry of drugs into various tissues; biodegradable polymers,
30 such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery after implantation (Emerich, DF *et al*, 1999, Cell Transplant, 8, 47-58) Alkermes, Inc. Cambridge, Mass.; and loaded nanoparticles, such as those made of

polybutylcyanoacrylate, which can deliver drugs across the blood brain barrier and can alter neuronal uptake mechanisms (Prog Neuropsychopharmacol Biol Psychiatry, 23, 941-949, 1999).

[0063] The invention also features the use of the composition comprising
5 surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, branched and unbranched or combinations thereof, or long-circulating liposomes or stealth liposomes). Nucleic acid molecules of the invention can also comprise covalently attached PEG molecules of various molecular weights. These formulations offer a method for increasing the accumulation of drugs in target
10 tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al.* Chem. Rev. 1995, 95, 2601-2627; Ishiwata *et al.*, Chem. Pharm. Bull. 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in
15 tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al.*, Science 1995, 267, 1275-1276; Oku *et al.*, 1995, Biochim. Biophys. Acta, 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to conventional cationic liposomes which are known to accumulate in
20 tissues of the MPS (Liu *et al.*, J. Biol. Chem. 1995, 42, 24864-24870; Choi *et al.*, International PCT Publication No. WO 96/10391; Ansell *et al.*, International PCT Publication No. WO 96/10390; Holland *et al.*, International PCT Publication No. WO 96/10392). Long-circulating liposomes are also likely to protect drugs from
25 nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid accumulation in metabolically aggressive MPS tissues such as the liver and spleen.

[0064] In a further embodiment, the present invention includes nucleic acid compositions, such as siRNA compositions, prepared as described in US 2003/0166601. In this regard, in one embodiment, the present invention provides a
30 composition of the siRNA described herein comprising: 1) a core complex comprising the nucleic acid (*e.g.*, siRNA) and polyethyleneimine; and 2) an outer shell moiety comprising NHS-PEG-VS and a targeting moiety.

[0065] In certain embodiments of the present invention a targeting moiety as described above is utilized to target the desired siRNA(s) to a cell of interest.

[0066] Thus, in certain embodiments, compositions comprising the siRNA molecules of the present invention include at least one targeting moiety, such as a
5 ligand for a cell surface receptor or other cell surface marker that permits highly specific interaction of the composition comprising the siRNA molecule (the “vector”) with the target tissue or cell. More specifically, in one embodiment, the vector preferably will include an unshielded ligand or a shielded ligand. The vector may include two or more targeting moieties, depending on the cell type that
10 is to be targeted. Use of multiple (two or more) targeting moieties can provide additional selectivity in cell targeting, and also can contribute to higher affinity and/or avidity of binding of the vector to the target cell. When more than one targeting moiety is present on the vector, the relative molar ratio of the targeting moieties may be varied to provide optimal targeting efficiency. Methods for
15 optimizing cell binding and selectivity in this fashion are known in the art. The skilled artisan also will recognize that assays for measuring cell selectivity and affinity and efficiency of binding are known in the art and can be used to optimize the nature and quantity of the targeting ligand(s).

[0067] Suitable ligands include, but are not limited to: RGD and monoclonal
20 antibodies against receptors on the surface of tumor cells or endothelial cells.

[0068] Another example of a targeting moiety is sialyl-Lewis^x, where the composition is intended for treating a region of inflammation. Other peptide ligands may be identified using methods such as phage display (F. Bartoli *et al.*, Isolation of peptide ligands for tissue-specific cell surface receptors, in Vector
25 Targeting Strategies for Therapeutic Gene Delivery (Abstracts from Cold Spring Harbor Laboratory 1999 meeting), 1999, p4) and microbial display (Georgiou *et al.*, Ultra-High Affinity Antibodies from Libraries Displayed on the Surface of Microorganisms and Screened by FACS, in Vector Targeting Strategies for
Therapeutic Gene Delivery (Abstracts from Cold Spring Harbor Laboratory 1999
30 meeting), 1999, p 3.). Ligands identified in this manner are suitable for use in the present invention.

[0069] Methods have been developed to create novel peptide sequences that elicit strong and selective binding for target tissues and cells such as “DNA Shuffling” (W. P. C. Stremmer, Directed Evolution of Enzymes and Pathways by DNA Shuffling, in Vector Targeting Strategies for Therapeutic Gene Delivery (Abstracts form Cold Spring Harbor Laboratory 1999 meeting), 1999, p.5.) and these novel sequence peptides are suitable ligands for the invention. Other chemical forms for ligands are suitable for the invention such as natural carbohydrates which exist in numerous forms and are a commonly used ligand by cells (Kraling *et al.*, Am. J. Path., 1997, 150, 1307) as well as novel chemical species, some of which may be analogues of natural ligands such as D-amino acids and peptidomimetics and others which are identified through medicinal chemistry techniques such as combinatorial chemistry (P. D. Kassner *et al.*, Ligand Identification via Expression (LIVE0): Direct selection of Targeting Ligands from Combinatorial Libraries, in Vector Targeting Strategies for Therapeutic Gene Delivery (Abstracts form Cold Spring Harbor Laboratory 1999 meeting), 1999, p8.).

[0070] In a further embodiment, the present invention includes nucleic acid compositions prepared for delivery as described in US Patent 7,163,695, US Patent No. 7,070,807 and US Patent 6,692,911. In this regard, in one embodiment, the present invention provides a nucleic acid of the present invention in a composition comprising the histidine-lysine copolymers (also referred to herein as PolyTran™) as described in US Patents 7,163,695, 7,070,807 and 6,692,911 either alone or in combination with PEG (e.g., branched or unbranched PEG or a mixture of both) or in combination with PEG and a targeting moiety.

[0071] The present invention also includes compositions prepared for storage or administration which include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington: The Science and Practice of Pharmacy, 20th Edition. Baltimore, MD: Lippincott Williams & Wilkins, 2000. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These

include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

[0072] A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors which those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

[0073] The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0074] The nucleic acid compositions of the invention can be used in combination with other nucleic acid compositions that target the same or different areas of the target gene (*e.g.*, EGFR), or that target other genes of interest. The nucleic acid compositions of the invention can also be used in combination with any of a variety of treatment modalities, such as chemotherapy, radiation therapy, or small molecule regimens.

[0075] Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically
5 elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch,
10 or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over
15 a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed.

[0076] Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein
20 the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0077] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose,
25 methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long
30 chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation

products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

5 [0078] Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and
10 flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0079] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with
15 a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

[0080] Pharmaceutical compositions of the invention can also be in the form of
20 oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products
25 of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

[0081] Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative and flavoring and coloring agents. The
30 pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that

have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and
5 isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0082] The nucleic acid molecules of the invention can also be administered in
10 the form of suppositories, *e.g.*, for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

15 [0083] Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

20 [0084] Dosage levels of the order of from about 0.01 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the disease conditions described herein (about 0.5 mg to about 7 g per patient or subject per day). The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated
25 and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

[0085] It is understood that the specific dose level for any particular patient or subject depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of
30 administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

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[0086] For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

[0087] The nucleic acid molecules of the present invention can also be administered to a subject in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

[0088] The nucleic acid-based inhibitors of the invention are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection or infusion pump, with or without their incorporation in biopolymers.

[0089] The nucleic acid molecules of the instant invention may be used in compositions comprising multiple nucleic acid molecules (siRNAs) targeting different target sequences within the EGFR gene or targeting sequences within other genes.

[0090] The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions associated with altered expression and/or activity of EGFR. Thus, the small nucleic acid molecules described herein are useful, for example, in providing compositions to prevent, inhibit, or reduce breast, lung, prostate, colorectal, brain, esophageal, bladder, pancreatic, cervical, head and neck, and ovarian cancer, melanoma, lymphoma, glioma, multidrug resistant cancers, and any other cancerous diseases and/or other disease states, conditions, or traits associated with EGFR gene expression or activity in a subject or organism.

[0091] The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can also be used to prevent diseases or conditions associated with altered activity and/or expression of EGFR

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in individuals that are suspected of being at risk for developing such a disease or condition. For example, to treat or prevent a disease or condition associated with the expression levels of EGFR, the subject having the disease or condition, or suspected of being at risk for developing the disease or condition, can be treated, or
5 other appropriate cells can be treated, as is evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment. Thus, the present invention provides methods for treating or preventing diseases or conditions which respond to the modulation of EGFR expression comprising administering to a subject in need thereof an effective
10 amount of a composition comprising one or more of the nucleic acid molecules of the invention, such as those set forth in SEQ ID NOs: 11-20 and 122-323. In one embodiment, the present invention provides methods for treating or preventing diseases associated with expression of EGFR comprising administering to a subject in need thereof an effective amount of any one or more of the nucleic acid
15 molecules of the invention, such as those provided in SEQ ID NOs: 11-20 and 122-323, such that the expression of EGFR in the subject is down-regulated, thereby treating or preventing the disease associated with expression of EGFR. In this regard, the compositions of the invention can be used in methods for treating or preventing breast, lung, prostate, colorectal, brain, esophageal, bladder, pancreatic,
20 cervical, head and neck, meningioma, kidney, endometrial, and ovarian cancer, melanoma, lymphoma, glioblastoma, multidrug resistant cancers, and any other cancerous diseases, or other conditions which respond to the modulation of EGFR expression.

[0092] In a further embodiment, the nucleic acid molecules of the invention, such
25 as siRNA, antisense or ribozymes, can be used in combination with other known treatments to treat conditions or diseases discussed herein. For example, the described molecules can be used in combination with one or more known therapeutic or diagnostic agents to treat breast, lung, prostate, colorectal, brain, esophageal, bladder, pancreatic, cervical, head and neck, meningioma, kidney,
30 endometrial, and ovarian cancer, melanoma, lymphoma, glioblastoma, multidrug resistant cancers, and any other cancerous diseases or other conditions which respond to the modulation of EGFR expression. In another embodiment, the

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nucleic acid molecules of the present invention can be used to treat lung cancer, kidney cancer, pancreas cancer, breast cancer, head and neck cancer, stomach cancer or colon cancer.

[0093] In certain embodiments, therapeutic agents that may be used in conjunction with the siRNA molecules of the present invention to treat a cancer as described herein may include agents such as, chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, cytokines, and irradiation. These drugs inhibit either the calcium dependent phosphatase calcineurin (cyclosporine and FK506) or inhibit the p70S6 kinase that is important for growth factor induced signaling (rapamycin). (Liu *et al.*, *Cell* 66:807-815, 1991; Henderson *et al.*, *Immun.* 73:316-321, 1991; Bierer *et al.*, *Curr. Opin. Immun.* 5:763-773, 1993). In a further embodiment, the RNA molecules of the present invention are administered to a patient in conjunction with (*e.g.*, before, simultaneously or following) bone marrow transplantation, T cell ablative therapy using either chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or antibodies such as OKT3 or CAMPATH. In another embodiment, the cell compositions of the present invention are administered following B-cell ablative therapy such as agents that react with CD20, *e.g.*, Rituxan.

[0094] In a further embodiment, the RNA molecules of the present invention can be modified according to US patent publication 2005/0186586, 2005/0181382 and/or 2006/0134787 by introducing one or more mismatch(s) into siRNA duplex by modifying the sequence of sense strand of siRNA, to, among other things, decrease the stability of the 5' antisense end of the molecule to preferentially guide the proper strand into the RISC complex or reduce off target effect. Additionally, the RNA molecules of the present invention can be modified according to US2005/0037988 by introducing wobble base pair (G/U) between antisense strand of siRNA and its complementary target mRNA, to, among other things, increase RISC turnover.

[0095] Compositions and methods are known in the art for identifying subjects having, or suspected of being at risk for having the diseases or disorders associated with expression of EGFR as described herein.

Examples

5 EXAMPLE 1: Antitumor efficacy from systemically delivered hEGFR-siRNA formulated with PolyTranTM in A431 model

[0096] Figure 3. Tumor inhibition effect of hEGFR-siRNA-PolyTranTM NPX on A431 tumor xenografts

[0097] Antitumor efficacy of PolyTranTM (PT-NPX) (Figure 6) carrying hEGFR-siRNA was determined in A431 xenograft model. Human epidermoid carcinoma A431 cells (5×10^6 cells per mouse) were implanted subcutaneously into female nude mice. Mice bearing established tumors were treated with intravenous administration of PolyTran NPX carrying hEGFR-siRNA (2 mg/kg, 1:1 mixture of hEGFR-25-1 and hEGFR-25-2) every other day for 6 times started on Day 4 post tumor cells implantation, when tumor size was around 80-100 mm³. PolyTran-siRNA NPX was prepared by mixing PolyTran peptide with siRNA at 3:1 ratio (w/w) and the particle size of NPX is around 100 nm. Treatment controls included no treatment (untreated) and Erlotinib (TarcevaTM, a FDA approved EGFR inhibitor) which was daily administered orally at 100 mg/kg for 6 days. Tumor size was measured every other day before administration of PT-siRNA NPX.

[0098] Treatment with PT-NPX carrying human EGFR siRNA at 2 mg/kg significantly inhibited A431 tumor growth in comparison with untreated control; and the inhibition effect was more profound than the TarcevaTM treatment control.

25 EXAMPLE 2: Antitumor efficacy from systemically delivered PT-siRNA NPX is hEGFR-siRNA specific and requires formulation of PT-NPX

[0099] Figure 4. Inhibition of A431 tumor growth by PT-EGFR-siRNA NPX is hEGFR-siRNA specific and requires formulation of PT-siRNA NPX

[0100] To confirm that the anti-tumor efficacy in Sample 1 is hEGFR-siRNA specific and requires formulation of siRNA with PT-NPX, PolyTranTM (PT-NPX) carrying hEGFR-siRNA or negative control-siRNA, as well as the PolyTran

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peptide alone or hEGFR-siRNA alone, were tested in A431 xenograft model. Human epidermoid carcinoma A431 cells (5×10^6 cells per mouse) were implanted subcutaneously into female nude mice. Mice bearing established tumors were treated with intravenous administration of PolyTran NPX carrying hEGFR-siRNA (2 mg/kg, 1:1 mixture of hEGFR-25-1 and hEGFR-25-2) or negative control-siRNA (2 mg/kg), or hEGFR-siRNA alone (2 mg/kg, 1:1 mixture of hEGFR-25-1 and hEGFR-25-2), or PolyTran peptide alone (6 mg/kg peptide) every other day for 4 times started on Day 5 post tumor cells implantation, when tumor size was around 80-100 mm³. PolyTran-siRNA NPX was prepared by mixing PolyTran peptide with siRNA at 3:1 ratio (w/w) and the particle size of NPX is around 100 nm. Treatment controls included no treatment (untreated). Tumor size was measured every other day before administration of testing articles.

[0101] Only the treatment with PT-NPX carrying human EGFR siRNA at 2 mg/kg significantly inhibited A431 tumor growth in comparison with untreated control. All other treatment groups include PT-NPX carrying control-siRNA, hEGFR-siRNA alone, or PolyTran peptide, did not inhibit A431 tumor growth.

EXAMPLE 3: Antitumor efficacy from systemically delivered hEGFR-siRNA formulated with PolyTranTM in A549 model

[0102] Figure 5. Tumor inhibition effect of hEGFR-siRNA-PolyTranTM NPX on A549 tumor xenografts

[0103] In addition to A431 model, the antitumor efficacy of PolyTranTM (PT-NPX) carrying hEGFR-siRNA was determined in A549 xenograft model. Human Non-small Cell Lung Cancer (NSCLC) A549 cells (5×10^6 cells per mouse) were implanted subcutaneously into female nude mice. Mice bearing established tumors were treated with intravenous administration of PolyTran NPX carrying hEGFR-siRNA (2 mg/kg, 1:1 mixture of hEGFR-25-1 and hEGFR-25-2) or negative control-siRNA (2 mg/kg) every other day for 6 times started on Day 9 post tumor cells implantation, when tumor size was around 80-100 mm³. PolyTran-siRNA NPX was prepared by mixing PolyTran peptide with siRNA at 3:1 ratio (w/w) and the particle size of NPX is around 100 nm. Treatment controls included no treatment (untreated) and Erlotinib (TarcevaTM, a FDA approved EGFR inhibitor)

which was daily administered orally at 100 mg/kg for 6 days. Tumor size was measured every other day before administration of PT-siRNA NPX.

[0104] Treatment with PT-NPX carrying human EGFR siRNA at 2 mg/kg significantly inhibited A549 tumor growth in comparison with untreated control; and the inhibition effect was more profound than the Tarceva™ treatment control. The PT-NPX carrying control-siRNA did not have inhibition effect on A549 tumor growth.

EXAMPLE 4: siRNA Molecules Inhibit Human EGFR Expression

[0105] Human EGFR 25-mer siRNA molecules were designed using the publicly available sequence for the human EGFR gene (NM_005228). Table 1 shows the target sequence of hEGFR-siRNA candidates.

[0106] Table 1: Target DNA Sequence of hEGFR-siRNA Candidates

SEQ ID NO:	hEGFR start position	DNA Sequence	Region	GC%
1	528	CACAGTGGAGCGAATTCCTTTGGAA	ORF	48.0
2	1246	CGCAAAGTGTGTAAACGGAATAGGTA	ORF	44.0
3	2438	GGATCCCAGAAGGTGAGAAAGTTAA	ORF	44.0
4	2789	CGCAGCATGTCAAGATCACAGATTT	ORF	44.0
5	2858	CAGAAGGAGGCAAAGTGCCTATCAA	ORF	48.0
6	2874	GCCTATCAAGTGGATGGCATTGGAA	ORF	48.0
7	3214	CCAAGTCCTACAGACTCCAATTCT	ORF	48.0
8	3355	TCTCTGAGTGCAACCAGCAACAATT	ORF	44.0
9	3435	CAGCTTCTTGCAGCGATACAGCTCA	ORF	52.0
10	3784	GAAGCCAAGCCAAATGGCATCTTTA	ORF	44.0

[0107] Candidate siRNA molecules were synthesized using standard techniques.

siRNA candidates are shown in Table 2.

[0108] Table 2: hEGFR siRNA Molecules

ID NO:	Name	siRNA sequence (sense strand/antisense strand)	SEQ ID NO:
07-25-001	hEGFR-25-1	5'-r(CACAGUGGAGCGAAUCCUUGGAA)-3'	11
		3'--(GUGUCACCUCGCUUAAGGAAACCUU)r-5'	12
07-25-002	hEGFR-25-2	5'-r(CGCAAAGUGUGUAACGGAAUAGGUA)-3'	13
		3'--(GCGUUUCACACAUUGCCUUAUCCAU)r-5'	14
07-25-003	hEGFR-25-3	5'-r(GGAUCCCAGAAGGUGAGAAAGUUAA)-3'	15
		3'--(CCUAGGGUCUUCCACUCUUUCAAUU)r-5'	16

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07-25-004	hEGFR-25-4	5'-r(CGCAGCAUGUCAAGAUCACAGAUUU)-3' 3'--(GCGUCGUACAGUUCUAGUGUCUAAA)r-5'	17 18
07-25-00	hEGFR-25-5	5'-r(CCAAGUCCUACAGACUCCAACUUCU)-3' 3'--(GGUUCAGGAUGUCUGAGGUUGAAGA)r-5'	19 20

[0109] The above candidates were screened *in vitro* for knockdown activity of the hEGFR gene. HT-29 cells were transfected using electroporation with the siRNA candidates (Table 2) and hEGFR protein expression was assayed at 72 hours post-transfection using a commercially available ELISA kit (see Figure 1).

5 [0110] Two siRNA candidates, hEGFR-25-1 and hEGFR-25-2, were further tested for activity in a dose titration experiment. As shown in Figure 2, these two hEGFR siRNA candidates inhibited hEGFR expression in a dose-dependent manner.

10 [0111] In summary, this experiment shows successful inhibition of EGFR expression by numerous siRNA candidates. These siRNA candidates can be used for the treatment of diseases.

EXAMPLE 5: siRNA Candidate Molecules for the Inhibition of Human EGFR Expression

15 [0112] Human EGFR 25-mer siRNA molecules were designed using a tested algorithm and using the publicly available sequences for human EGFR gene (NM_005228). Table 3 shows the target sequence of hEGFR-siRNA candidates.

[0113] Table 3: Target DNA Sequence of hEGFR-siRNA Candidates

SE Q ID NO:	hEGFR start postion	DNA Sequence	Region	GC %
21	91	5'TGCCAAGGCACGAGTAACAAGCTCA3'	5'UTR	52
22	98	5'GCACGAGTAACAAGCTCACGCAGTT3'	5'UTR	52
23	194	5'TGGAAATTACCTATGTGCAGAGGAA3'	5'UTR	40
24	195	5'GGAAATTACCTATGTGCAGAGGAAT3'	5'UTR	40
25	196	5'GAAATTACCTATGTGCAGAGGAATT3'	5'UTR	36
26	201	5'TACCTATGTGCAGAGGAATTATGAT3'	5'UTR	36
27	203	5'CCTATGTGCAGAGGAATTATGATCT3'	5'UTR	40

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28	209	5'TGCAGAGGAATTATGATCTTTCCTT3'	5'UTR	36
29	211	5'CAGAGGAATTATGATCTTTCCTTCT3'	5'UTR	36
30	346	5'TCCTATGCCTTAGCAGTCTTATCTA3'	ORF	40
31	347	5'CCTATGCCTTAGCAGTCTTATCTAA3'	ORF	40
32	353	5'CCTTAGCAGTCTTATCTAACTATGA3'	ORF	36
33	494	5'GGGACATAGTCAGCAGTGACTTTCT3'	ORF	48
34	500	5'TAGTCAGCAGTGACTTTCTCAGCAA3'	ORF	44
35	887	5'CCCGTAATTATGTGGTGACAGATCA3'	ORF	44
36	888	5'CCGTAATTATGTGGTGACAGATCAC3'	ORF	44
37	966	5'CGTCCGCAAGTGTAAGAAGTGCGAA3'	ORF	52
38	972	5'CAAGTGTAAGAAGTGCGAAGGGCCT3'	ORF	52
39	994	5'CCTTGCCGCAAAGTGTAACGGAA 3'	ORF	52
40	999	5'CCGCAAAGTGTAACGGAATAGGT3'	ORF	48
41	1000	5'CGCAAAGTGTAACGGAATAGGTA3'	ORF	44
42	1001	5'GCAAAGTGTAACGGAATAGGTAT3'	ORF	40
43	1002	5'CAAAGTGTAACGGAATAGGTATT3'	ORF	36
44	1043	5'CACTCTCCATAAATGCTACGAATAT3'	ORF	36
45	1156	5'CCTCTGGATCCACAGGAAGTGGATA3'	ORF	52
46	1160	5'TGGATCCACAGGAAGTGGATATTCT3'	ORF	44
47	1250	5'TCCATGCCTTTGAGAACCTAGAAAT3'	ORF	40
48	1284	5'CAGGACCAAGCAACATGGTCAGTTT3'	ORF	48
49	1309	5'TCTCTTGCAGTCGTCAGCCTGAACA3'	ORF	52
50	1337	5'CATCCTTGGGATTACGCTCCCTCAA3'	ORF	52
51	1355	5'CCCTCAAGGAGATAAGTGATGGAGA3'	ORF	48
52	1356	5'CCTCAAGGAGATAAGTGATGGAGAT3'	ORF	44
53	1358	5'TCAAGGAGATAAGTGATGGAGATGT3'	ORF	40
54	1361	5'AGGAGATAAGTGATGGAGATGTGAT3'	ORF	40
55	1362	5'GGAGATAAGTGATGGAGATGTGATA3'	ORF	40
56	1363	5'GAGATAAGTGATGGAGATGTGATAA3'	ORF	36
57	1636	5'CCAAGGGAGTTTGTGGAGAACTCTG3'	ORF	52

58	1642	5'GAGTTTGTGGAGAACTCTGAGTGCA3'	ORF	48
59	1727	5'CAGACAACTGTATCCAGTGTGCCCA3'	ORF	52
60	1735	5'TGTATCCAGTGTGCCCACTACATTG3'	ORF	48
61	1861	5'CATCCAAACTGCACCTACGGATGCA3'	ORF	52
62	2171	5'GCACGGTGTATAAGGGACTCTGGAT3'	ORF	52
63	2222	5'CCGTCGCTATCAAGGAATTAAGAGA3'	ORF	44
64	2223	5'CGTCGCTATCAAGGAATTAAGAGAA3'	ORF	40
65	2226	5'CGCTATCAAGGAATTAAGAGAAGCA3'	ORF	40
66	2232	5'CAAGGAATTAAGAGAAGCAACATCT3'	ORF	36
67	2272	5'GAAATCCTCGATGAAGCCTACGTGA3'	ORF	48
68	2542	5'CCGCAGCATGTCAAGATCACAGATT3'	ORF	48
69	2543	5'CGCAGCATGTCAAGATCACAGATTT3'	ORF	44
70	2608	5'CATGCAGAAGGAGGCAAAGTGCCTA3'	ORF	52
71	2612	5'CAGAAGGAGGCAAAGTGCCTATCAA3'	ORF	48
72	2624	5'AAGTGCCTATCAAGTGGATGGCATT3'	ORF	44
73	2628	5'GCCTATCAAGTGGATGGCATTGGAA3'	ORF	48
74	2629	5'CCTATCAAGTGGATGGCATTGGAAT3'	ORF	44
75	2634	5'CAAGTGGATGGCATTGGAATCAATT3'	ORF	40
76	2803	5'CAGCCACCCATATGTACCATCGATG3'	ORF	52
77	2807	5'CACCCATATGTACCATCGATGTCTA3'	ORF	44
78	2815	5'TGTACCATCGATGTCTACATGATCA3'	ORF	40
79	2858	5'TAGACGCAGATAGTCGCCCAAAGTT3'	ORF	48
80	2968	5'CCAAGTCCTACAGACTCCAACCTTCT3'	ORF	48
81	2969	5'CAAGTCCTACAGACTCCAACCTTCTA3'	ORF	44
82	2981	5'ACTCCAACCTTCTACCGTGCCCTGAT3'	ORF	52
83	3109	5'TCTCTGAGTGCAACCAGCAACAATT3'	ORF	44
84	3129	5'CAATTCCACCGTGGCTTGCATTGAT3'	ORF	48
85	3134	5'CCACCGTGGCTTGCATTGATAGAAA3'	ORF	48
86	3135	5'CACCGTGGCTTGCATTGATAGAAAT3'	ORF	44
87	3145	5'TGCATTGATAGAAATGGGCTGCAAA3'	ORF	40

88	3146	5'GCATTGATAGAAATGGGCTGCAAAG3'	ORF	44
89	3189	5'CAGCTTCTTGCAGCGATACAGCTCA3'	ORF	52
90	3262	5'CCAGTGCCTGAATACATAAACCAGT3'	ORF	44
91	3431	5'CCACCTGTGTCAACAGCACATTTCGA3'	ORF	52
92	3472	5'GCCCAGAAAGGCAGCCACCAAATTA3'	ORF	52
93	3473	5'CCCAGAAAGGCAGCCACCAAATTAG3'	ORF	52
94	3537	5'GGAAGCCAAGCCAAATGGCATCTTT3'	ORF	48
95	3538	5'GAAGCCAAGCCAAATGGCATCTTTA3'	ORF	44
96	3539	5'AAGCCAAGCCAAATGGCATCTTTAA3'	ORF	40
97	3552	5'TGGCATCTTTAAGGGCTCCACAGCT3'	ORF	52
98	3555	5'CATCTTTAAGGGCTCCACAGCTGAA3'	ORF	48
99	3634	5'CCACGGAGGATAGTATGAGCCCTAA3'	ORF	52
100	3635	5'CACGGAGGATAGTATGAGCCCTAAA3'	ORF	48
101	3846	5'TACAGAAACGCATCCAGCAAGAATA3'	ORF	40
102	4327	5'TGATGGACCAGTGGTTTCCAGTCAT3'	3'UTR	48
103	4335	5'CAGTGGTTTCCAGTCATGAGCGTTA3'	3'UTR	48
104	4432	5'CAGCAAGAGAGGATGACACATCAAA3'	3'UTR	44
105	4471	5'CCAGCCCACATTGGATTCATCAGCA3'	3'UTR	52
106	4472	5'CAGCCCACATTGGATTCATCAGCAT3'	3'UTR	48
107	4474	5'GCCCACATTGGATTCATCAGCATTT3'	3'UTR	44
108	4510	5'CCACAGCTGAGAATGTGGAATACCT3'	3'UTR	48
109	4511	5'CACAGCTGAGAATGTGGAATACCTA3'	3'UTR	44
110	4570	5'TCTCCTAATTTGAGGCTCAGATGAA3'	3'UTR	40
111	4581	5'GAGGCTCAGATGAAATGCATCAGGT3'	3'UTR	48
112	4879	5'CAGGTGCGAATGACAGTAGCATTAT3'	3'UTR	44
113	4884	5'GCGAATGACAGTAGCATTATGAGTA3'	3'UTR	40
114	4892	5'CAGTAGCATTATGAGTAGTGTGGAA3'	3'UTR	40
115	4897	5'GCATTATGAGTAGTGTGGAATTCAG3'	3'UTR	40
116	4905	5'AGTAGTGTGGAATTCAGGTAGTAAA3'	3'UTR	36
117	5079	5'TGTGCCCTGTAACCTGACTGGTTAA3'	3'UTR	48

118	5337	5'CCTGACTGGTTAACAGCAGTCCTTT3'	3'UTR	48
119	5340	5'GACTGGTTAACAGCAGTCCTTTGTA3'	3'UTR	44
120	5350	5'CAGCAGTCCTTTGTAAACAGTGTTT3'	3'UTR	40
121	5442	5'CAGCCTACAGTTATGTTTCAGTCACA3'	3'UTR	44

[0114] hEGFR candidate siRNA molecules are shown in Table 4 below and are set forth in SEQ ID NOs: 122-323.

[0115] Table 4: hEGFR Candidate siRNA Molecules

ID NO:	Name	siRNA sequence (sense strand/antisense strand)	SEQ ID NO:
07-25-021	hEGFR-25-21	5'-r(UGCCAAGGCACGAGUAACAAGCUCA) -3'	122
		3'- (ACGGUUCCGUGCUCAUUGUUCGAGU)r-5'	123
07-25-022	hEGFR-25-22	5'-r(GCACGAGUAACAAGCUCACGCAGUU) -3'	124
		3'- (CGUGCUCAUUGUUCGAGUGCGUCAA)r-5'	125
07-25-023	hEGFR-25-23	5'-r(UGGAAAUUACCUAUGUGCAGAGGAA) -3'	126
		3'- (ACCUUUA AUGGAUACACGUCUCCUU)r-5'	127
07-25-024	hEGFR-25-24	5'-r(GGAAAUUACCUAUGUGCAGAGGAAU) -3'	128
		3'- (CCUUUA AUGGAUACACGUCUCCUUA)r-5'	129
07-25-025	hEGFR-25-25	5'-r(GAAAUUACCUAUGUGCAGAGGAAUU) -3'	130
		3'- (CUUUAAUGGAUACACGUCUCCUUA)r-5'	131
07-25-026	hEGFR-25-26	5'-r(UACCUAUGUGCAGAGGAAUUAUGAU) -3'	132
		3'- (AUGGAUACACGUCUCCUUA AUACUA)r-5'	133
07-25-027	hEGFR-25-27	5'-r(CCUAUGUGCAGAGGAAUUAUGAUCU) -3'	134
		3'- (GGAUACACGUCUCCUUA AUACUAGA)r-5'	135
07-25-028	hEGFR-25-28	5'-r(UGCAGAGGAAUUAUGAUCUUUCCUU) -3'	136
		3'- (ACGUCUCCUUA AUACUAGAAAGGAA)r-5'	137
07-25-029	hEGFR-25-29	5'-r(CAGAGGAAUUAUGAUCUUUCCUUCU) -3'	138
		3'- (GUCUCCUUA AUACUAGAAAGGAAGA)r-5'	139
07-25-	hEGFR-	5'-r(UCCUAUGCCUUAGCAGUCUUAUCUA) -3'	140

030	25-30	3'- (AGGAUACGGAAUCGUCAGAAUAGAU)r-5'	141
07-25-031	hEGFR-25-31	5'-r(CCUAUGCCUUAGCAGUCUUAUCUAA) -3'	142
		3'- (GGAUACGGAAUCGUCAGAAUAGAUU)r-5'	143
07-25-032	hEGFR-25-32	5'-r(CCUUAGCAGUCUUAUCUAAACUAUGA) -3'	144
		3'- (GGAAUCGUCAGAAUAGAUUGAUACU)r-5'	145
07-25-033	hEGFR-25-33	5'-r(GGGACAUAAGUCAGCAGUGACUUUCU) -3'	146
		3'-(CCCUGUAUCAGUCGUCACUGAAAGA)r-5'	147
07-25-034	hEGFR-25-34	5'-r(UAGUCAGCAGUGACUUUCUCAGCAA) -3'	148
		3'-(AUCAGUCGUCACUGAAAGAGUCGUU)r-5'	149
07-25-035	hEGFR-25-35	5'-r(CCCGUAAUUAUGUGGUGACAGAUCA) -3'	150
		3'- (GGGCAUUAUACACCACUGUCUAGU)r-5'	151
07-25-036	hEGFR-25-36	5'-r(CCGUAAUUAUGUGGUGACAGAUAC) -3'	152
		3'- (GGCAUUAUACACCACUGUCUAGUG)r-5'	153
07-25-037	hEGFR-25-37	5'-r(CGUCCGCAAGUGUAAGAAGUGCGAA) -3'	154
		3- (GCAGGCGUUCACAUUCUUCACGCUU)r-5'	155
07-25-038	hEGFR-25-38	5'-r(CAAGUGUAAGAAGUGCGAAGGGCCU) -3'	156
		3'- (GUUCACAUUCUUCACGCUUCCCGGA)r-5'	157
07-25-039	hEGFR-25-39	5'-r(CCUUGCCGCAAAGUGUGUAACGGAA) -3'	158
		3'- (GGAACGGCGUUUCACACAUAUGCCUU)r-5'	159
07-25-040	hEGFR-25-40	5'-r(CCGCAAAGUGUGUAACGGAAUAGGU) -3'	160
		3'- (GGCGUUUCACACAUAUGCCUUAUCCA)r-5'	161
07-25-041	hEGFR-25-41	5'-r(CGCAAAGUGUGUAACGGAAUAGGUA) -3'	162
		3'- (GCGUUUCACACAUAUGCCUUAUCCA)r-5'	163
07-25-042	hEGFR-25-42	5'-r(GCAAAGUGUGUAACGGAAUAGGUAU) -3'	164
		3'- (CGUUUCACACAUAUGCCUUAUCCAUA)r-5'	165
07-25-043	hEGFR-25-43	5'-r(CAAAGUGUGUAACGGAAUAGGUAUU) -3'	166
		3'- (GUUUCACACAUAUGCCUUAUCCAUA)r-5'	167
07-25-044	hEGFR-25-44	5'-r(CACUCUCCAUAUAAUGCUACGAAUAU) -3'	168
		3'- (GUGAGAGGUAUUUACGAUGCUUAUA)r-5'	169
07-25-	hEGFR-	5'-r(CCUCUGGAUCCACAGGAACUGGAUA) -3'	170

045	25-45	3'-(GGAGACCUAGGUGUCCUUGACCUAU)r-5'	171
07-25-046	hEGFR-25-46	5'-r(UGGAUCCACAGGAACUGGAUAUUCU) -3'	172
		3'-(ACCUAGGUGUCCUUGACCUAUAAGA)r-5'	173
07-25-047	hEGFR-25-47	5'-r(UCCAUGCCUUUGAGAACCUAGAAAU) -3'	174
		3'-(AGGUACGGAAACUCUUGGAUCUUUA)r-5'	175
07-25-048	hEGFR-25-48	5'-r(CAGGACCAAGCAACAUGGUCAGUUU) -3'	176
		3'-(GUCCUGGUUCGUUGUACCAGUCAA)r-5'	177
07-25-049	hEGFR-25-49	5'-r(UCUCUUGCAGUCGUCAGCCUGAACA) -3'	178
		3'-(AGAGAACGUCAGCAGUCGGACUUGU)r-5'	179
07-25-050	hEGFR-25-50	5'-r(CAUCCUUGGGAUUACGCUCCCUCAA) -3'	180
		3'-(GUAGGAACCCUAAUGCGAGGGAGUU)r-5'	181
07-25-051	hEGFR-25-51	5'-r(CCCUCAAGGAGAUAAAGUGAUGGAGA) -3'	182
		3'-(GGGAGUUCCUCUAUUCACUACCUCU)r-5'	183
07-25-052	hEGFR-25-52	5'-r(CCUCAAGGAGAUAAAGUGAUGGAGAU) -3'	184
		3'-(GGAGUUCCUCUAUUCACUACCUCUA)r-5'	185
07-25-053	hEGFR-25-53	5'-r(UCAAGGAGAUAAAGUGAUGGAGAUGU) -3'	186
		3'-(AGUUCCUCUAUUCACUACCUCUACA)r-5'	187
07-25-054	hEGFR-25-54	5'-r(AGGAGAUAAAGUGAUGGAGAUGUGAU) -3'	188
		3'-(UCCUCUAUUCACUACCUCUACACUA)r-5'	189
07-25-055	hEGFR-25-55	5'-r(GGAGAUAAAGUGAUGGAGAUGUGAUA) -3'	190
		3'-(CCUCUAUUCACUACCUCUACACUAU)r-5'	191
07-25-056	hEGFR-25-56	5'-r(GAGAUAAAGUGAUGGAGAUGUGAUAA) -3'	192
		3'-(CUCUAUUCACUACCUCUACACUAUU)r-5'	193
07-25-057	hEGFR-25-57	5'-r(CCAAGGGAGUUUGUGGAGAACUCUG) -3'	194
		3'-(GGUUCCCUCAAACACCUCUUGAGAC)r-5'	195
07-25-058	hEGFR-25-58	5'-r(GAGUUUGUGGAGAACUCUGAGUGCA) -3'	196
		3'-(CUCAAACACCUCUUGAGACUCACGU)r-5'	197
07-25-059	hEGFR-25-59	5'-r(CAGACAACUGUAUCCAGUGUGCCCA) -3'	198
		3'-(GUCUGUUGACAUAGGUCACACGGGU)r-5'	199
07-25-	hEGFR-	5'-r(UGUAUCCAGUGUGCCCACUACAUG) -3'	200

060	25-60	3'- (ACAUAGGUCACACGGGUGAUGUAAC)r-5'	201
07-25-061	hEGFR-25-61	5'-r(CAUCCAAACUGCACCUACGGAUGCA) -3'	202
		3'- (GUAGGUUUGACGUGGAUGCCUACGU)r-5'	203
07-25-062	hEGFR-25-62	5'-r(GCACGGUGUAUAAGGGACUCUGGAU) -3'	204
		3'- (CGUGCCACAUAUUCCCUGAGACCUA)r-5'	205
07-25-063	hEGFR-25-63	5'-r(CCGUCGCUAUCAAGGAAUUAAGAGA) -3'	206
		3'- (GGCAGCGAUAGUUCCUUAUUCUCU)r-5'	207
07-25-064	hEGFR-25-64	5'-r(CGUCGCUAUCAAGGAAUUAAGAGAA) -3'	208
		3'- (GCAGCGAUAGUUCCUUAUUCUCUU)r-5'	209
07-25-065	hEGFR-25-65	5'-r(CGCUAUCAAGGAAUUAAGAGAAGCA) -3'	210
		3'- (GCGAUAGUUCCUUAUUCUCUUCGU)r-5'	211
07-25-066	hEGFR-25-66	5'-r(CAAGGAAUUAAGAGAAGCAACAUCU) -3'	212
		3'- (GUUCCUUAUUCUCUUCGUUGUAGA)r-5'	213
07-25-067	hEGFR-25-67	5'-r(GAAAUCCUCGAUGAAGCCUACGUGA) -3'	214
		3'- (CUUUAGGAGCUACUUCGGAUGCACU)r-5'	215
07-25-068	hEGFR-25-68	5'-r(CCGCAGCAUGUCAAGAUCACAGAUU) -3'	216
		3'- (GGCGUCGUACAGUUCUAGUGUCUAA)r-5'	217
07-25-069	hEGFR-25-69	5'-r(CGCAGCAUGUCAAGAUCACAGAUUU) -3'	218
		3'- (GCGUCGUACAGUUCUAGUGUCUAAA)r-5'	219
07-25-070	hEGFR-25-70	5'-r(CAUGCAGAAGGAGGCAAAGUGCCUA) -3'	220
		3'- (GUACGUCUUCCUCCGUUUCACGGAU)r-5'	221
07-25-071	hEGFR-25-71	5'-r(CAGAAGGAGGCAAAGUGCCUAUCAA) -3'	222
		3'- (GUCUUCCUCCGUUUCACGGAUAGUU)r-5'	223
07-25-072	hEGFR-25-72	5'-r(AAGUGCCUAUCAAGUGGAUGGCAUU) -3'	224
		3'- (UUCACGGAUAGUUCACCUACCGUAA)r-5'	225
07-25-073	hEGFR-25-73	5'-r(GCCUAUCAAGUGGAUGGCAUUGGAA) -3'	226
		3'- (CGGAUAGUUCACCUACCGUAACCUU)r-5'	227
07-25-074	hEGFR-25-74	5'-r(CCUAUCAAGUGGAUGGCAUUGGAAU) -3'	228
		3'- (GGAUAGUUCACCUACCGUAACCUUA)r-5'	229
07-25-	hEGFR-	5'-r(CAAGUGGAUGGCAUUGGAAUCAAUU) -3'	230

075	25-75	3'- (GUUCACCUACCGUAACCUUAGUUA)r-5'	231
07-25-076	hEGFR-25-76	5'-r(CAGCCACCCAUAUGUACCAUCGAUG) -3'	232
		3'- (GUCGGUGGGUAUACAUGGUAGCUAC)r-5'	233
07-25-077	hEGFR-25-77	5'-r(CACCCAUAUGUACCAUCGAUGUCUA) -3'	234
		3'- (GUGGGUAUACAUGGUAGCUACAGAU)r-5'	235
07-25-078	hEGFR-25-78	5'-r(UGUACCAUCGAUGUCUACAUGAUCA) -3'	236
		3'- (ACAUGGUAGCUACAGAUAGUACUAGU)r-5'	237
07-25-079	hEGFR-25-79	5'-r(UAGACGCAGAUAGUCGCCCAAAGUU) -3'	238
		3'- (AUCUGCGUCUAUCAGCGGGUUUCAA)r-5'	239
07-25-080	hEGFR-25-80	5'-r(CCAAGUCCUACAGACUCCAACUUCU) -3'	240
		3'- (GGUUCAGGAUGUCUGAGGUUGAAGA)r-5'	241
07-25-081	hEGFR-25-81	5'-r(CAAGUCCUACAGACUCCAACUUCUA) -3'	242
		3'- (GUUCAGGAUGUCUGAGGUUGAAGAU)r-5'	243
07-25-082	hEGFR-25-82	5'-r(ACUCCAACUUCUACCGUGCCCUGAU) -3'	244
		3'- (UGAGGUUGAAGAUGGCACGGGACUA)r-5'	245
07-25-083	hEGFR-25-83	5'-r(UCUCUGAGUGCAACCAGCAACAAUU) -3'	246
		3'- (AGAGACUCACGUUGGUCGUUGUUA)r-5'	247
07-25-084	hEGFR-25-84	5'-r(CAAUUCCACCGUGGCUUGCAUUGAU) -3'	248
		3'- (GUUAAGGUGGCACCGAACGUAACUA)r-5'	249
07-25-085	hEGFR-25-85	5'-r(CCACCGUGGCUUGCAUUGAUAGAAA) -3'	250
		3'- (GGUGGCACCGAACGUAACUAUCUUU)r-5'	251
07-25-086	hEGFR-25-86	5'-r(CACCGUGGCUUGCAUUGAUAGAAAU) -3'	252
		3'- (GUGGCACCGAACGUAACUAUCUUUA)r-5'	253
07-25-087	hEGFR-25-87	5'-r(UGCAUUGAUAGAAAUGGGCUGCAA) -3'	254
		3'- (ACGUAACUAUCUUUACCCGACGUUU)r-5'	255
07-25-088	hEGFR-25-88	5'-r(GCAUUGAUAGAAAUGGGCUGCAAAG) -3'	256
		3'- (CGUAACUAUCUUUACCCGACGUUUC)r-5'	257
07-25-089	hEGFR-25-89	5'-r(CAGCUUCUUGCAGCGAUACAGCUCA) -3'	258
		3'- (GUCGAAGAACGUCGCUAUGUCGAGU)r-5'	259
07-25-	hEGFR-	5'-r(CCAGUGCCUGAAUACAUAACCAGU) -3'	260

090	25-90	3'-(GGUCACGGACUUAUGUAUUUUGGUCA)r-5'	261
07-25-091	hEGFR-25-91	5'-r(CCACCUGUGUCAACAGCACAUUCGA)-3'	262
		3'-(GGUGGACACAGUUGUCGUGUAAGCU)r-5'	263
07-25-092	hEGFR-25-92	5'-r(GCCCAGAAAGGCAGCCACCAAUUA)-3'	264
		3'-(CGGGUCUUUCCGUCGGUGGUUUAAU)r-5'	265
07-25-093	hEGFR-25-93	5'-r(CCCAGAAAGGCAGCCACCAAUAG)-3'	266
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07-25-097	hEGFR-25-97	5'-r(UGGCAUCUUUAAGGGCUCCACAGCU)-3'	274
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07-25-098	hEGFR-25-98	5'-r(CAUCUUUAAGGGCUCCACAGCUGAA)-3'	276
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07-25-099	hEGFR-25-99	5'-r(CCACGGAGGAUAGUAUGAGCCCUAA)-3'	278
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07-25-100	hEGFR-25-100	5'-r(CACGGAGGAUAGUAUGAGCCCUAAA)-3'	280
		3'-(GUGCCUCCUAUCAUACUCGGGAUUU)r-5'	281
07-25-101	hEGFR-25-101	5'-r(UACAGAAACGCAUCCAGCAAGAAUA)-3'	282
		3'-(AUGUCUUUGCGUAGGUCGUUCUUAU)r-5'	283
07-25-102	hEGFR-25-102	5'-r(UGAUGGACCAGUGGUUUCAGUCAU)-3'	284
		3'-(ACUACCUGGUCACCAAAGGUCAGUA)r-5'	285
07-25-103	hEGFR-25-103	5'-r(CAGUGGUUUCAGUCAUGAGCGUUA)-3'	286
		3'-(GUCACCAAAGGUCAGUACUCGCAAU)r-5'	287
07-25-104	hEGFR-25-104	5'-r(CAGCAAGAGAGGAUGACACAUCAAA)-3'	288
		3'-(GUCGUUCUCUCCUACUGUGUAGUUU)r-5'	289
07-25-	hEGFR-	5'-r(CCAGCCCACAUUGGAUUCAUCAGCA)-3'	290

105	25-105	3'- (GGUCGGGUGUAACCUAAGUAGUCGU)r-5'	291
07-25-106	hEGFR-25-106	5'-r(CAGCCCACAUUGGAUUCAUCAGCAU) -3'	292
		3'- (GUCGGGUGUAACCUAAGUAGUCGUA)r-5'	293
07-25-107	hEGFR-25-107	5'-r(GCCCACAUUGGAUUCAUCAGCAUUU) -3'	294
		3'- (CGGGUGUAACCUAAGUAGUCGUAAA)r-5'	295
07-25-108	hEGFR-25-108	5'-r(CCACAGCUGAGAAUGUGGAAUACCU) -3'	296
		3'- (GGUGUCGACUCUUACACCUUAUGGA)r-5'	297
07-25-109	hEGFR-25-109	5'-r(CACAGCUGAGAAUGUGGAAUACCUA) -3'	298
		3'- (GUGUCGACUCUUACACCUUAUGGAU)r-5'	299
07-25-110	hEGFR-25-110	5'-r(UCUCCUAAUUUGAGGCUCAGAUGAA) -3'	300
		3'- (AGAGGAUUAAACUCCGAGUCUACUU)r-5'	301
07-25-111	hEGFR-25-111	5'-r(GAGGCUCAGAUGAAAUGCAUCAGGU) -3'	302
		3'- (CUCCGAGUCUACUUUACGUAGUCCA)r-5'	303
07-25-112	hEGFR-25-112	5'-r(CAGGUGCGAAUGACAGUAGCAUUUAU) -3'	304
		3'- (GUCCACGCUUACUGUCAUCGUAAUA)r-5'	305
07-25-113	hEGFR-25-113	5'-r(GCGAAUGACAGUAGCAUUAUGAGUA) -3'	306
		3'- (CGCUUACUGUCAUCGUAAUACUCAU)r-5'	307
07-25-114	hEGFR-25-114	5'-r(CAGUAGCAUUAUGAGUAGUGUGGAA) -3'	308
		3'- (GUCAUCGUAAUACUCAUCACACCUU)r-5'	309
07-25-115	hEGFR-25-115	5'-r(GCAUUAUGAGUAGUGUGGAAUUCAG) -3'	310
		3'- (CGUAAUACUCAUCACACCUUAAGUC)r-5'	311
07-25-116	hEGFR-25-116	5'-r(AGUAGUGUGGAAUUCAGGUAGUAAA) -3'	312
		3'- (UCAUCACACCUUAAGUCCAUCAUUU)r-5'	313
07-25-117	hEGFR-25-117	5'-r(UGUGCCCUGUAACCUGACUGGUUAA) -3'	314
		3'- (ACACGGGACAUUGGACUGACCAAUU)r-5'	315
07-25-118	hEGFR-25-118	5'-r(CCUGACUGGUUAAACAGCAGUCCUUU) -3'	316
		3'- (GGACUGACCAAUUGUCGUCAGGAAA)r-5'	317
07-25-119	hEGFR-25-119	5'-r(GACUGGUUAAACAGCAGUCCUUUGUA) -3'	318
		3'- (CUGACCAAUUGUCGUCAGGAAACAU)r-5'	319
07-25-	hEGFR-	5'-r(CAGCAGUCCUUUGUAAACAGUGUUU) -3'	320

120	25-120	3'- (GUCGUCAGGAAACAUAUUGUCACAAA)r-5'	321
07-25-121	hEGFR-25-121	5'-r(CAGCCUACAGUUAUGUUCAGUCACA) -3'	322
		3'- (GUCGGAUGUCAAUACAAGUCAGUGU)r-5'	323

[0116] The candidate siRNA molecules described in this Example can be used for inhibition of expression of hEGFR and are useful in a variety of therapeutic settings, for example, in the treatment of cardiovascular disorders such as aortic valve disease and cancers including but not limited to breast, lung, prostate, colorectal, brain, esophageal, bladder, pancreatic, cervical, head and neck, meningioma, kidney, endometrial, and ovarian cancer, melanoma, lymphoma, glioblastoma, multidrug resistant cancers, and any other cancerous diseases, and/or other disease states, conditions, or traits associated with hEGFR gene expression or activity in a subject or organism.

10

[0117] All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety.

15 [0118] From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

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SEQUENCE TABLE

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15

What is Claimed is:

1. A nucleic acid molecule that down regulates expression of an epidermal growth factor receptor (EGFR) gene, wherein the nucleic acid molecule comprises a nucleic acid that targets any one of the polynucleotide sequences set forth in SEQ ID NOs: 1-10 or 21-121.
2. The nucleic acid molecule of claim 1, wherein the nucleic acid is a short interfering RNA (siRNA) molecule.
3. The nucleic acid of claim 2, wherein the siRNA comprises any one of the single stranded RNA sequences provided in SEQ ID NOs: 11-20 and 122-323, or a double-stranded RNA thereof.
4. The nucleic acid molecule of claim 1, wherein the nucleic acid molecule down regulates expression of an EGFR gene via RNA interference (RNAi).
5. A composition comprising any one or more of the siRNA molecules of claim 3.
6. The composition of claim 5 further comprising a targeting moiety.
7. The composition of claim 5 further comprising a histidine-lysine copolymer.
8. A method for treating or preventing a cancer in a subject with an EGFR-expressing cancer and having or suspected of being at risk for having the cancer, comprising administering to the subject the composition of claim 5, thereby treating or preventing the cancer.
9. The method of claim 8 wherein the cancer is selected from the group consisting of breast cancer, lung cancer, prostate cancer, colorectal cancer, brain cancer, esophageal cancer, stomach cancer, bladder cancer, pancreatic cancer, cervical cancer, head and neck cancer, kidney cancer,

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- 5 endometrial cancer, ovarian cancer, meningioma, melanoma, lymphoma, and glioblastoma.

10. A method for reducing the synthesis or expression of EGFR in a cell, comprising introducing into the cell one or more siRNAs, wherein the one or more siRNAs have a sequence as set forth in SEQ ID NOs: 11-20 or 122-323.

human EGF receptor expression in HT-29 cells
(72 hours post-transfection by 25mer-hEGFR-siRNAs)

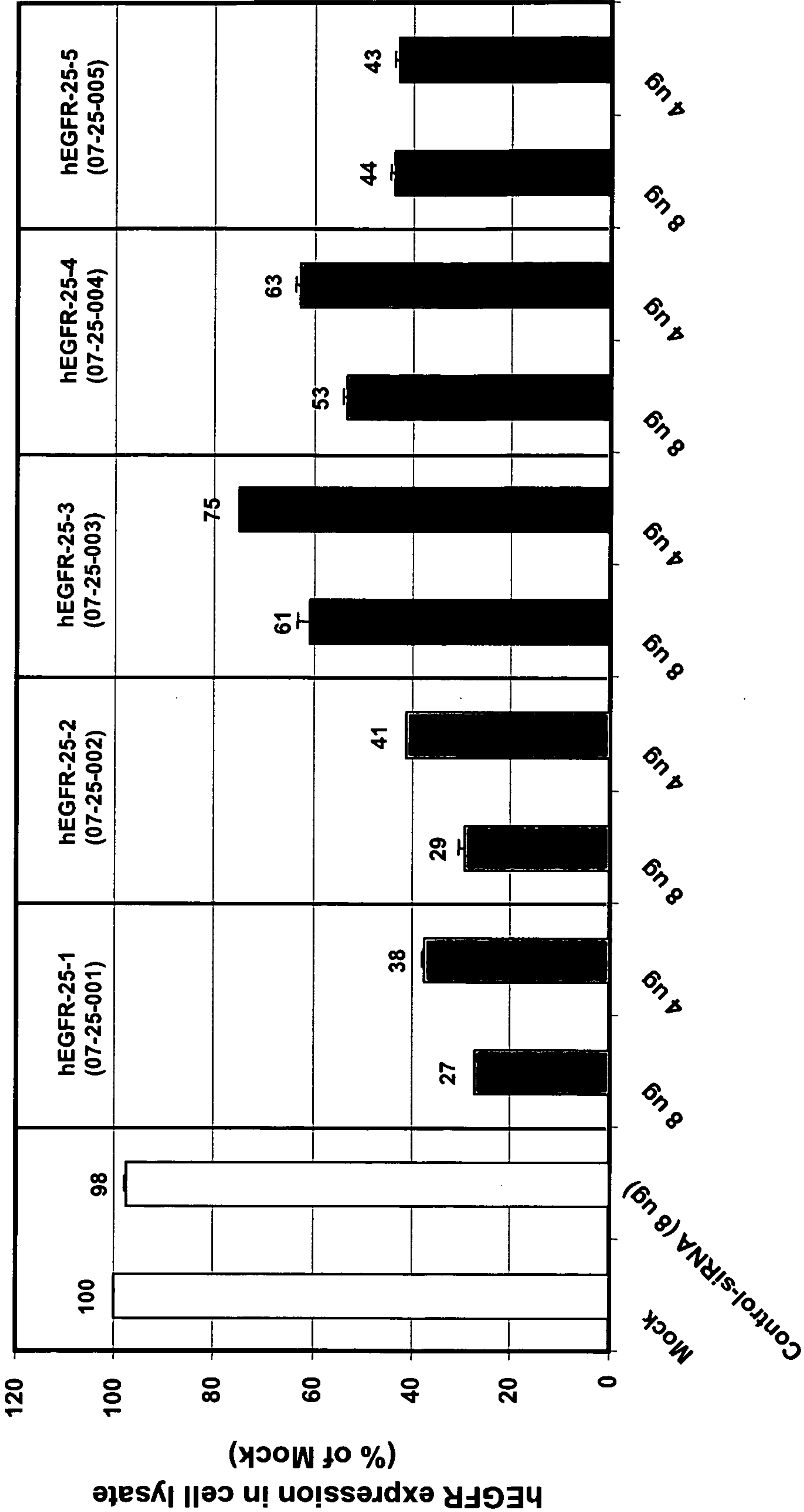


Figure 1

human EGF receptor expression in HT-29 cells (48 hours post-transfection
by different concentration of 25mer-hEGFR-siRNA)

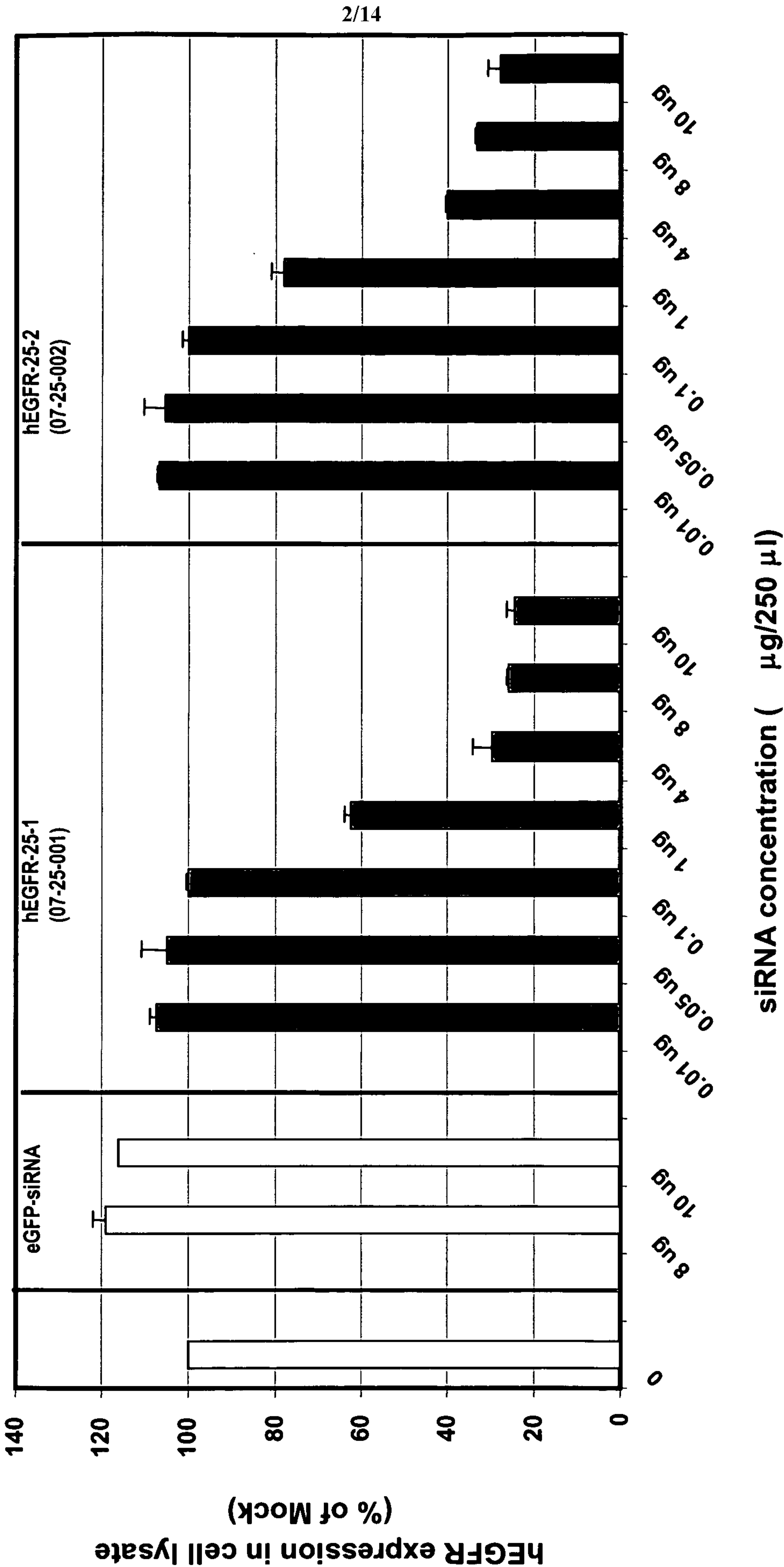


Figure 2

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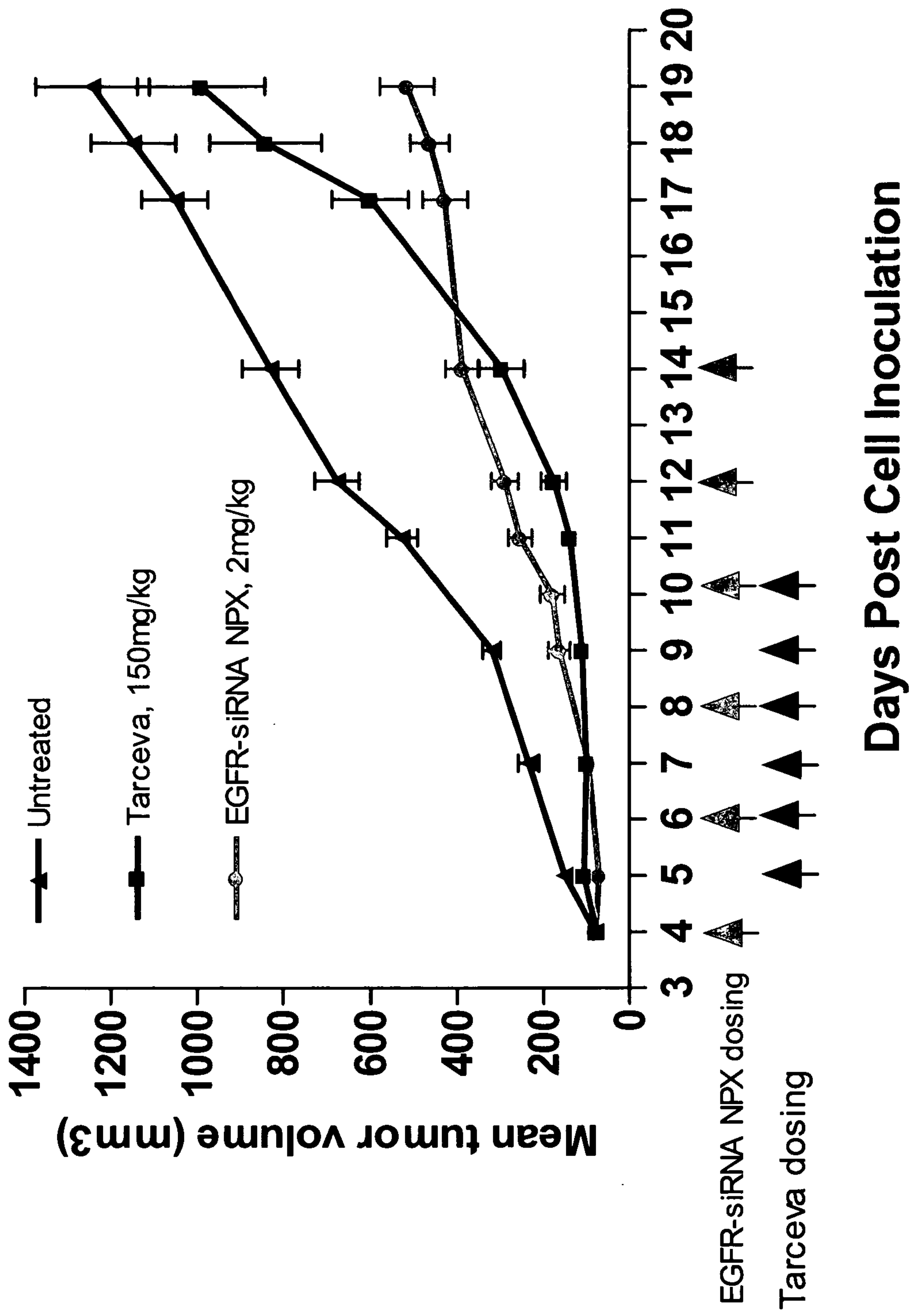


Figure 3

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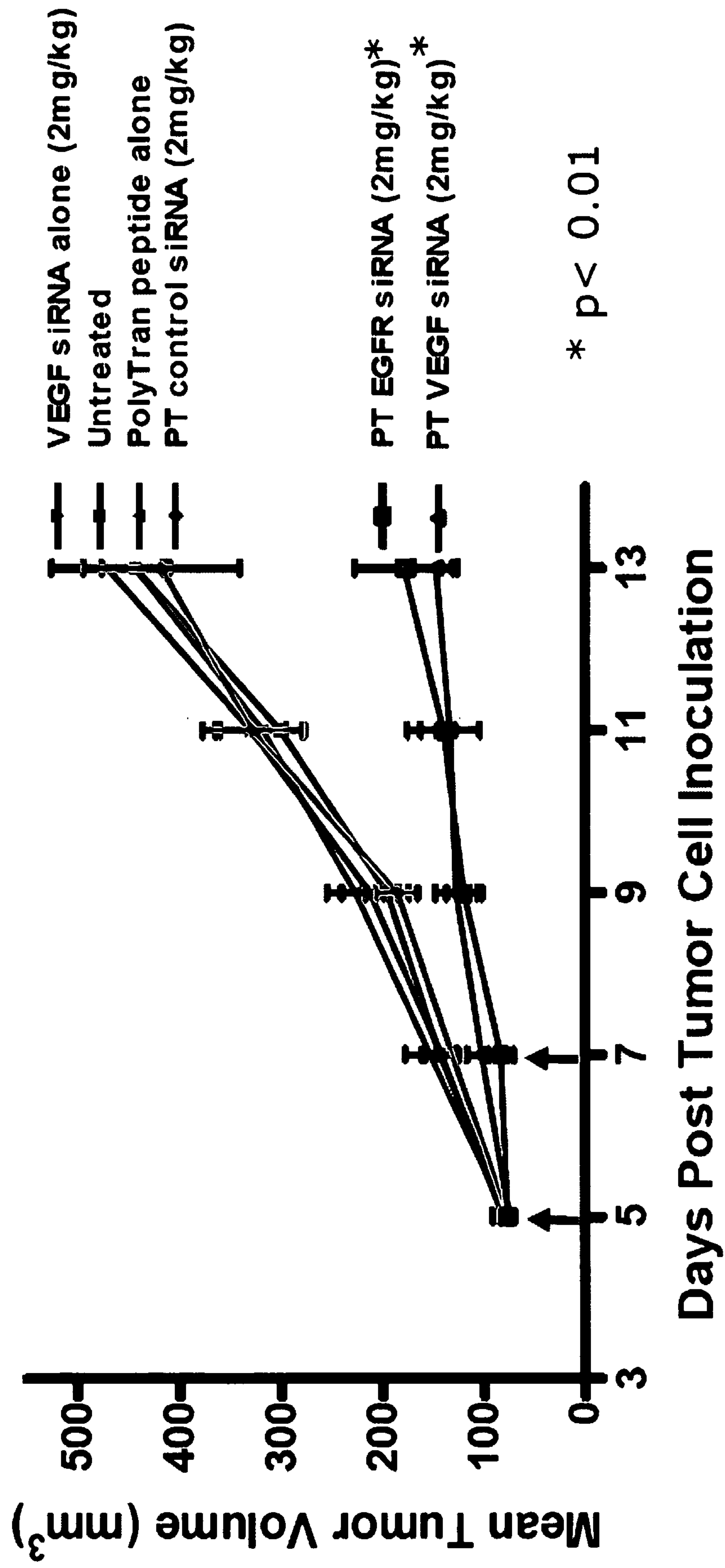


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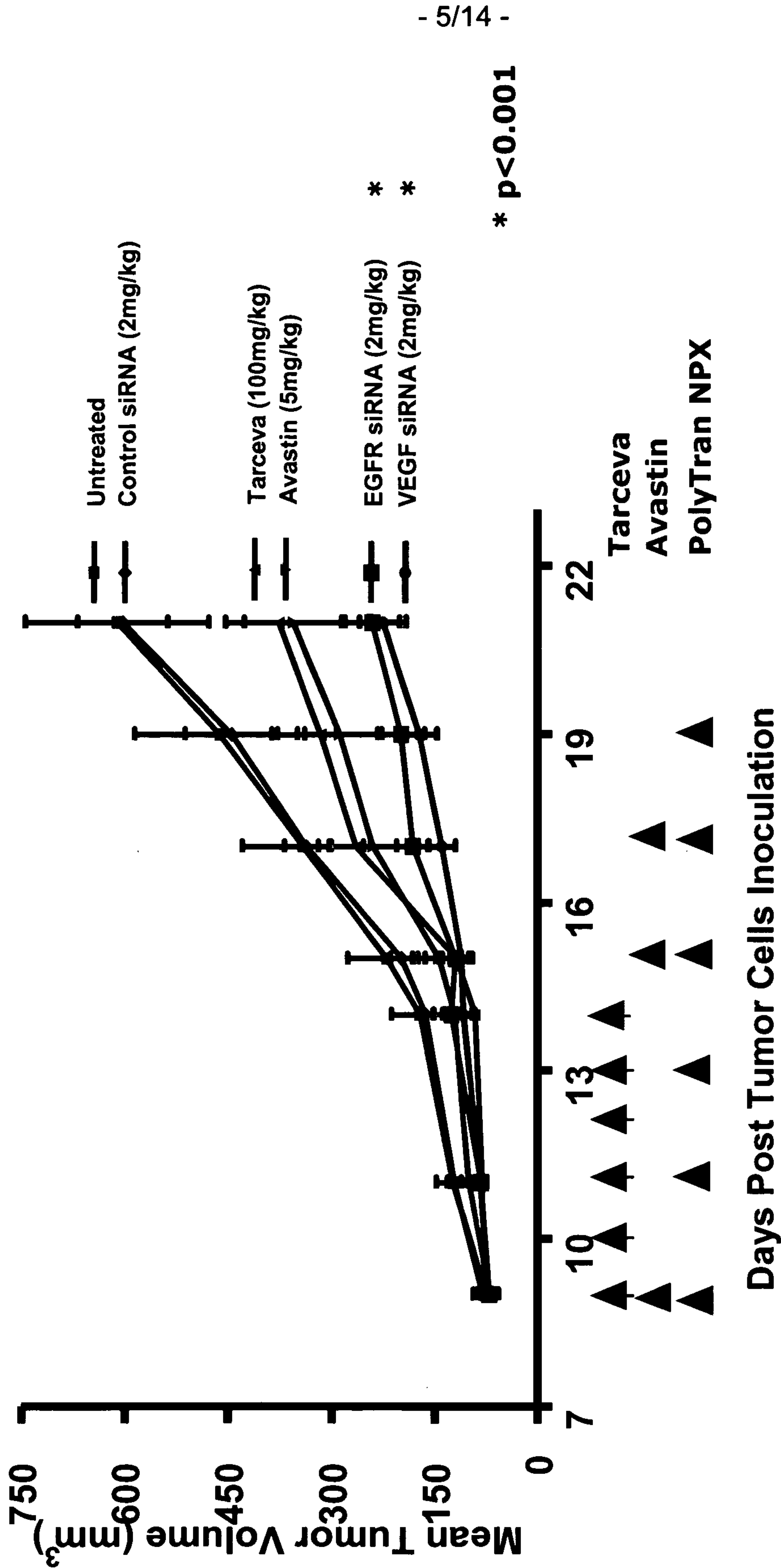


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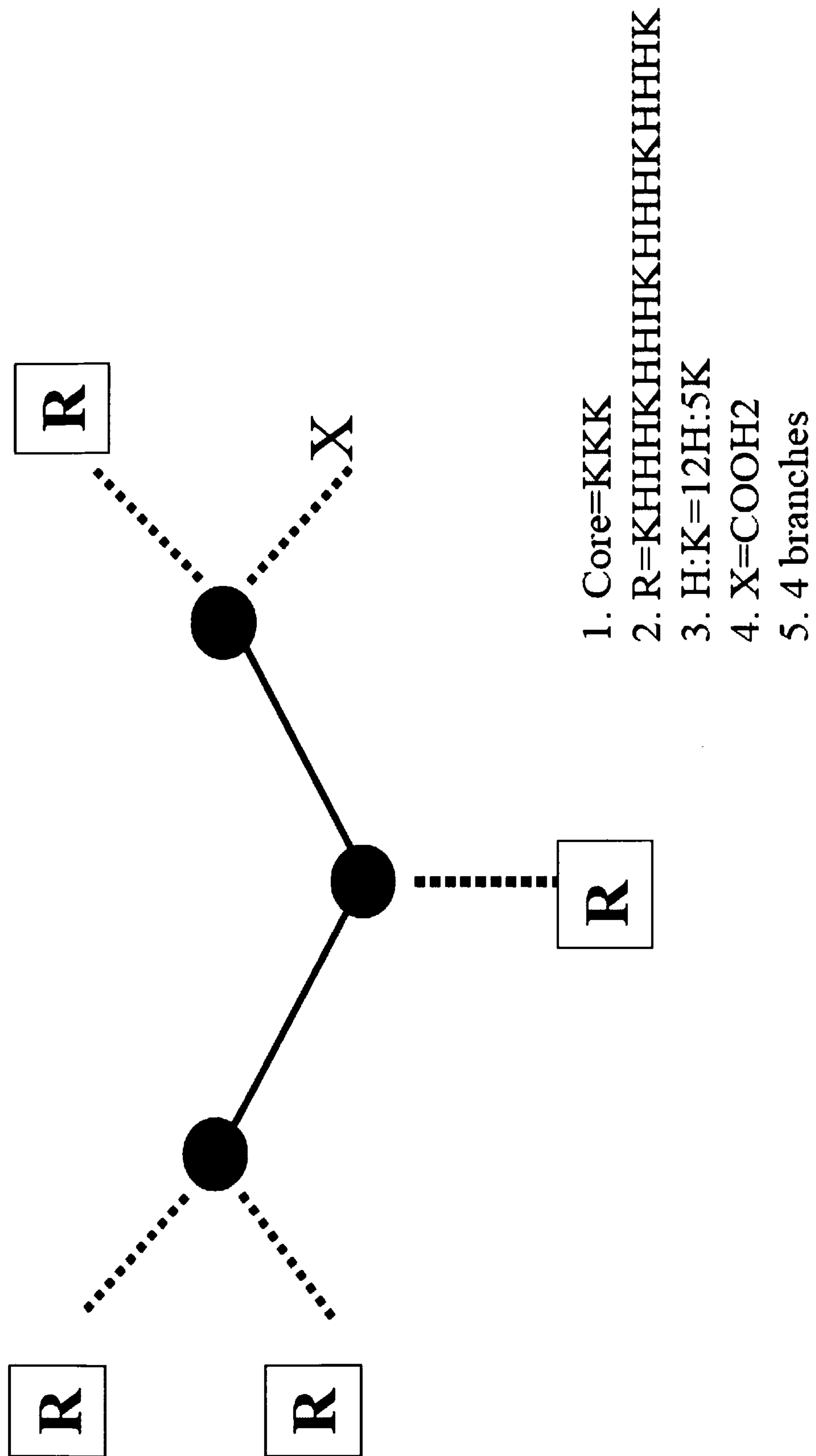


Figure 6

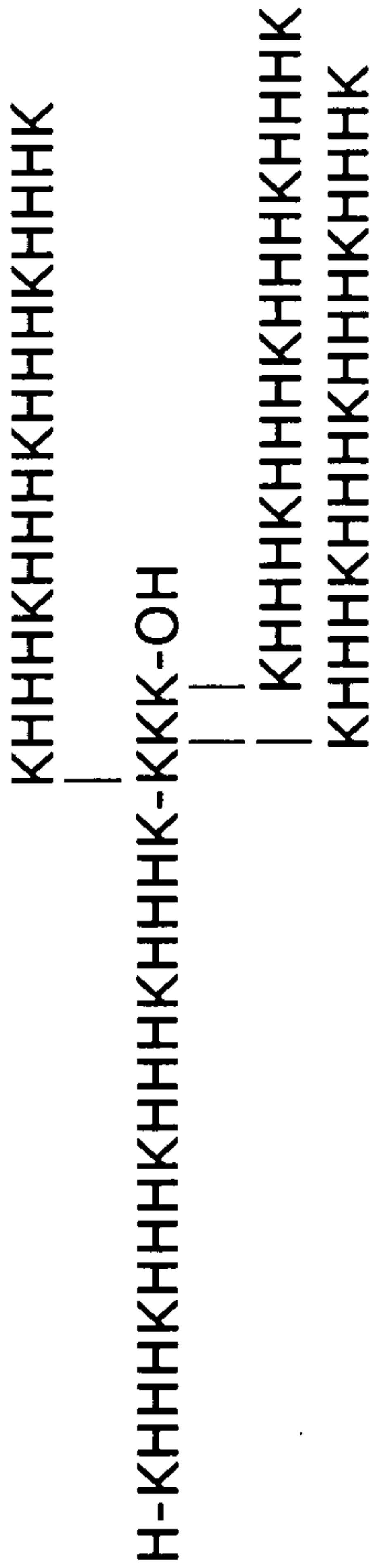


Figure 7

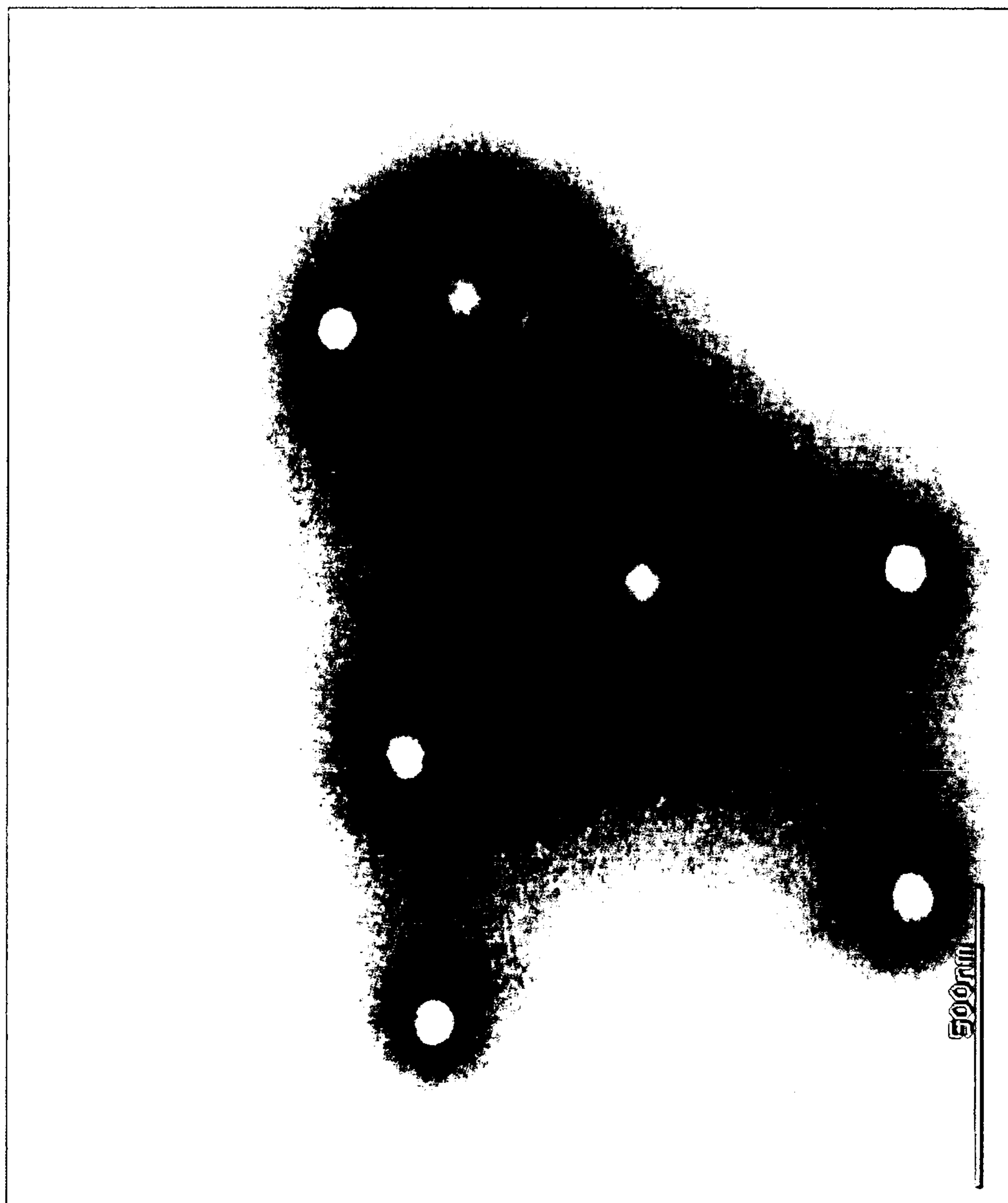
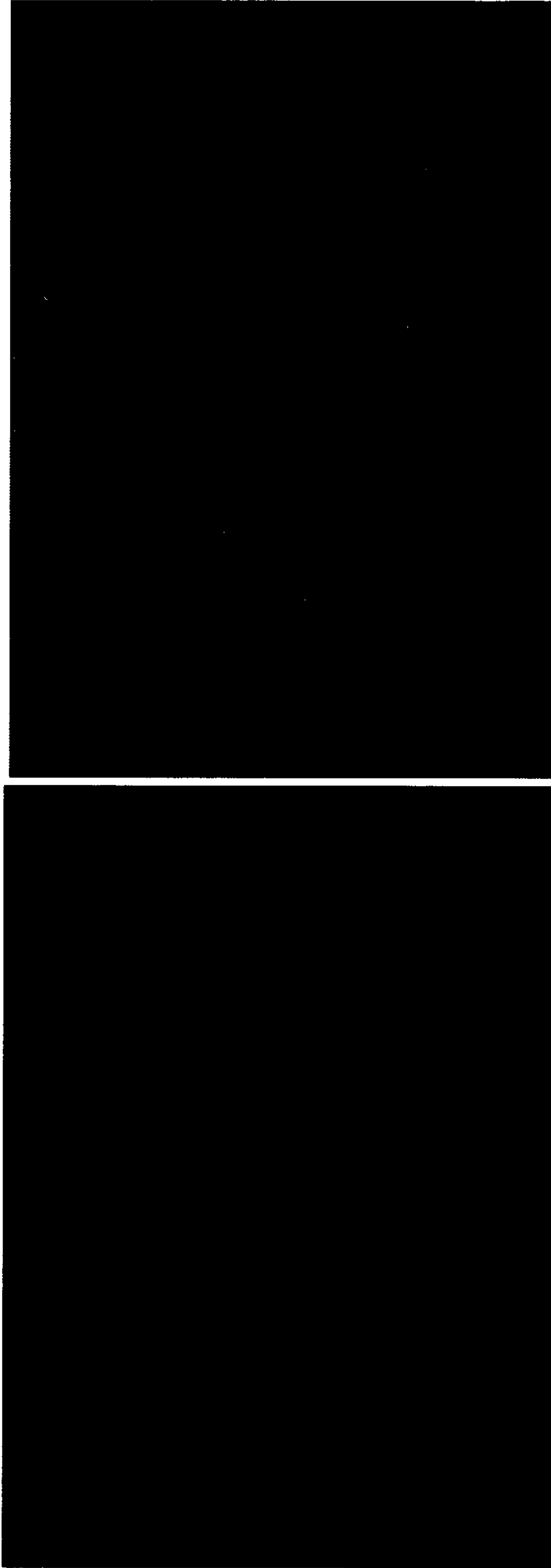


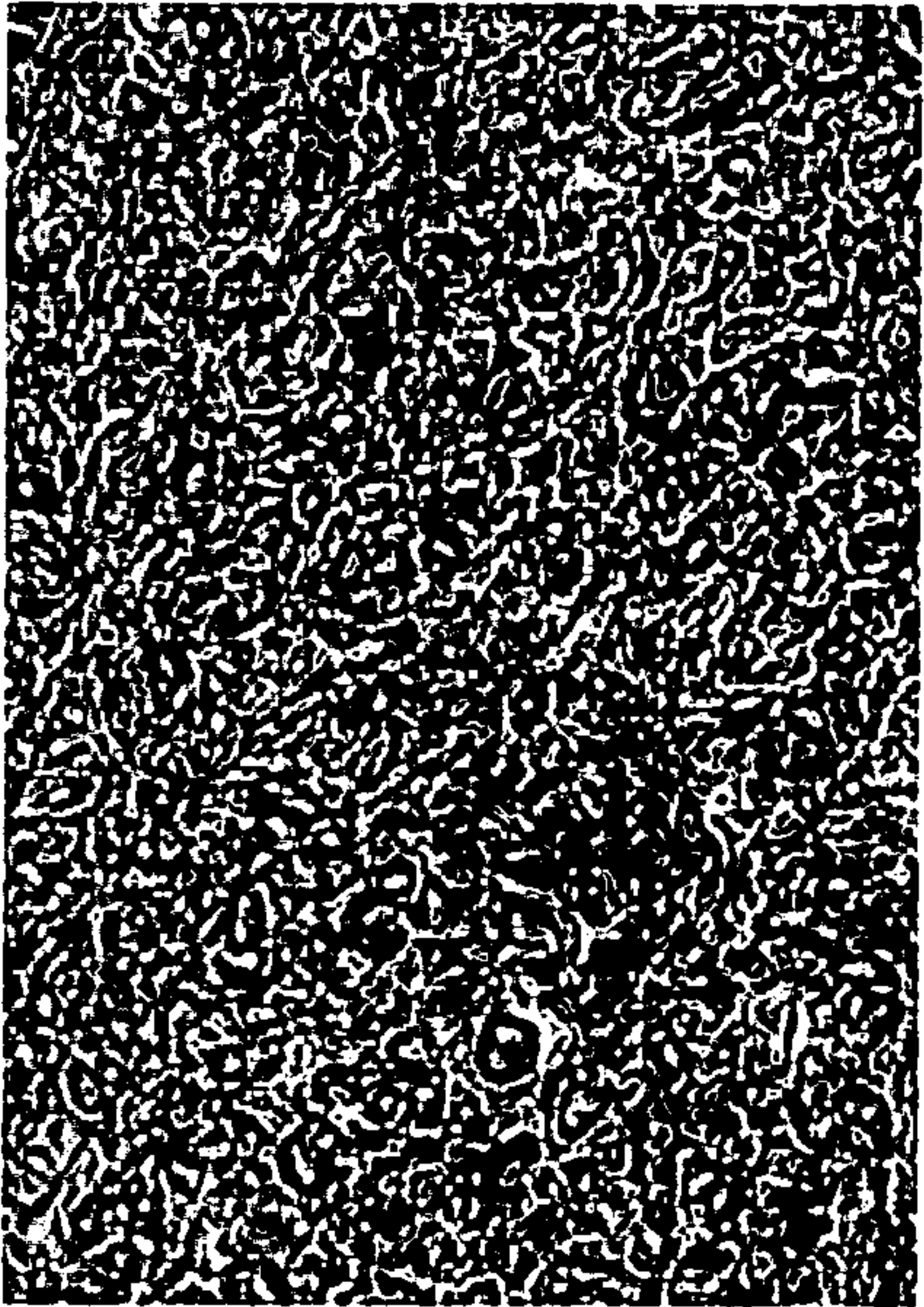
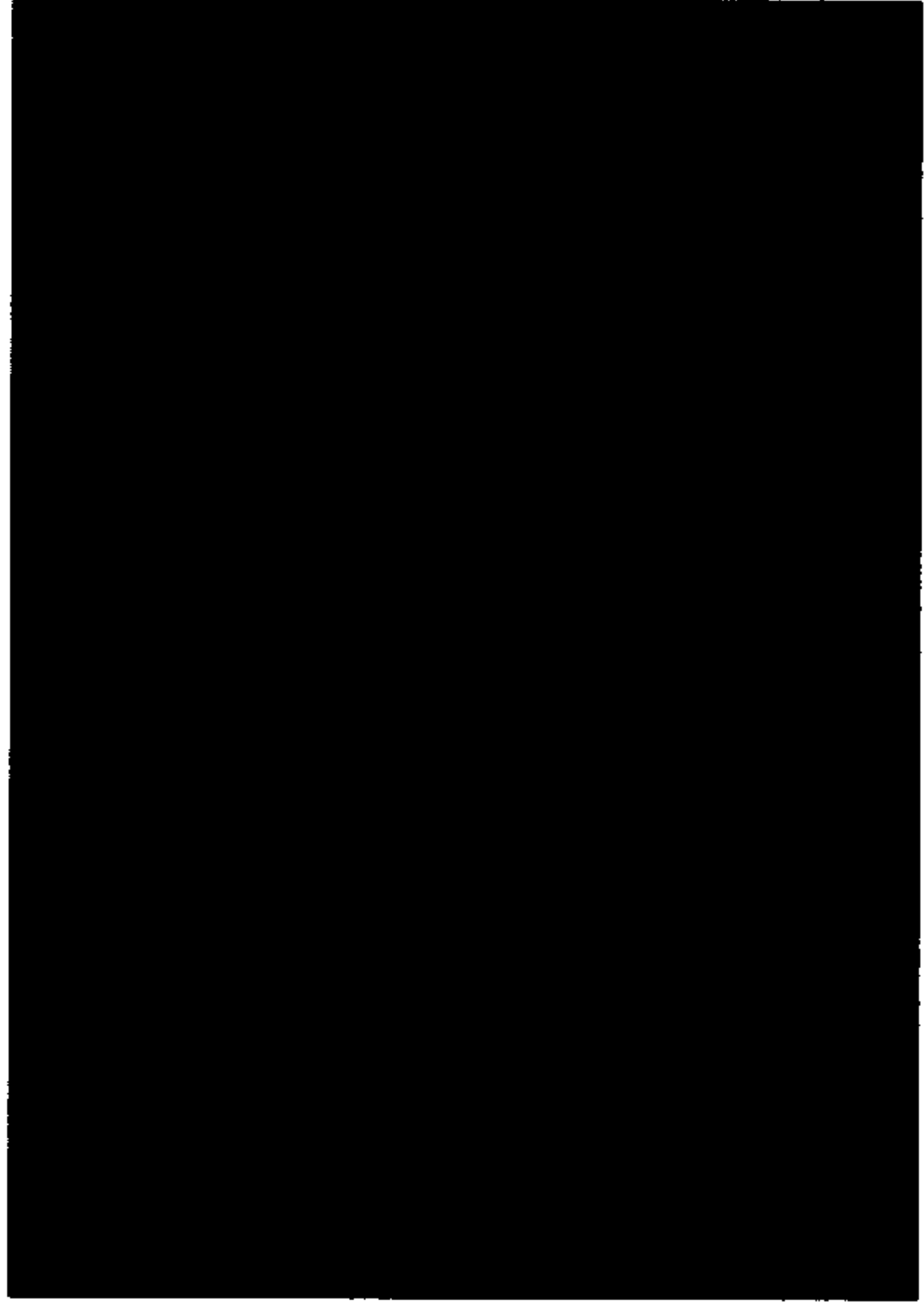
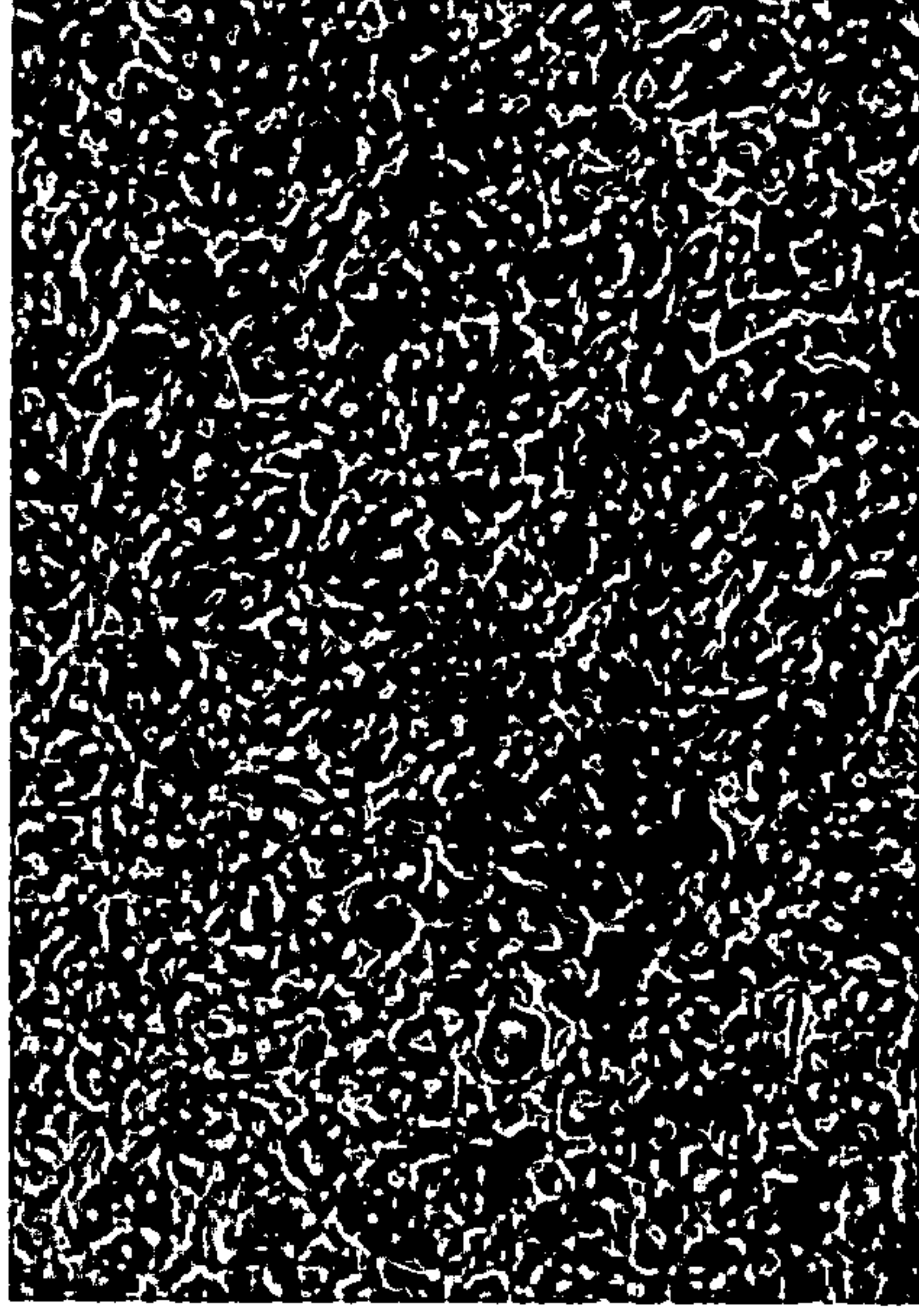
Figure 8



Fluorescent **Bright Field**

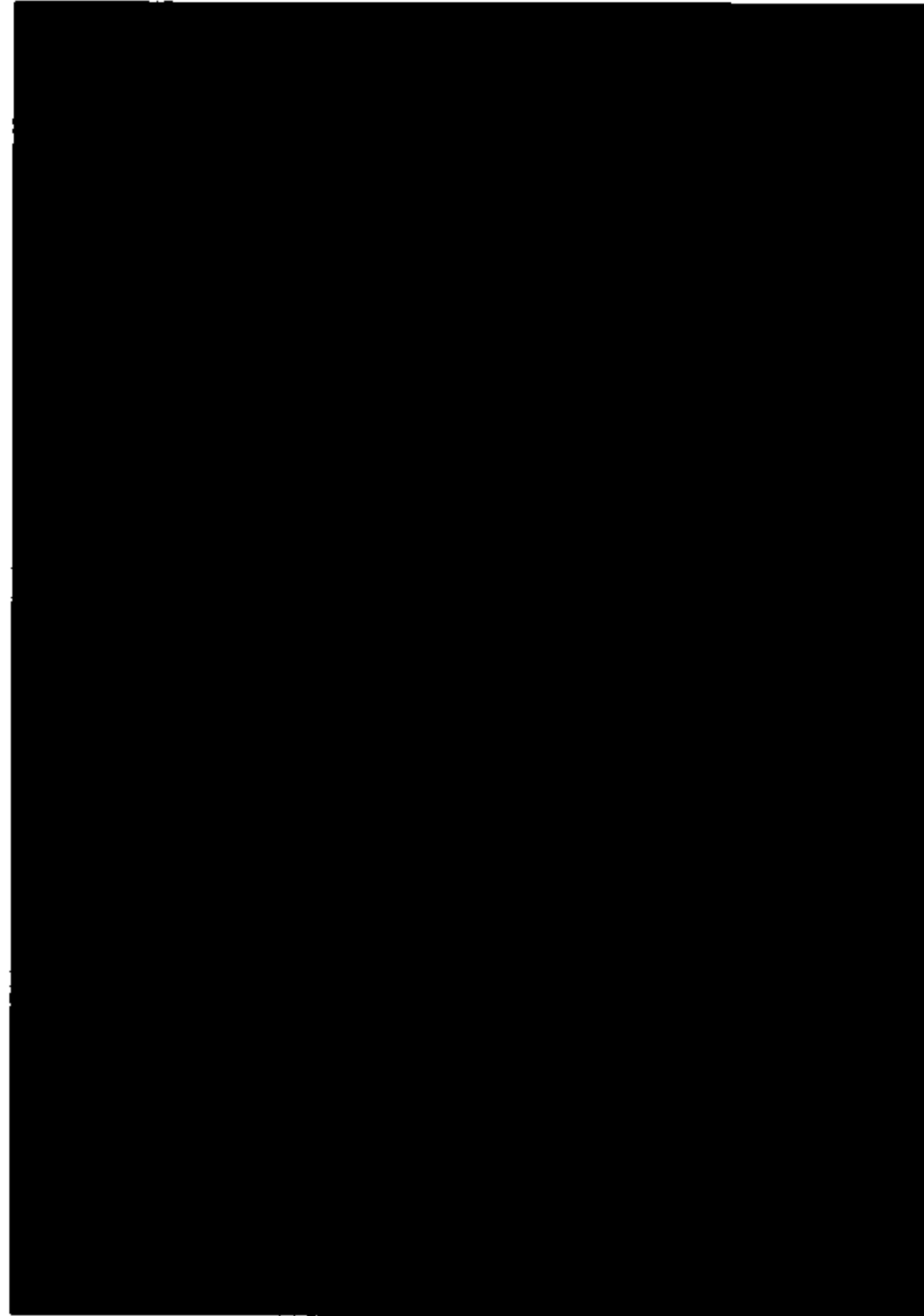
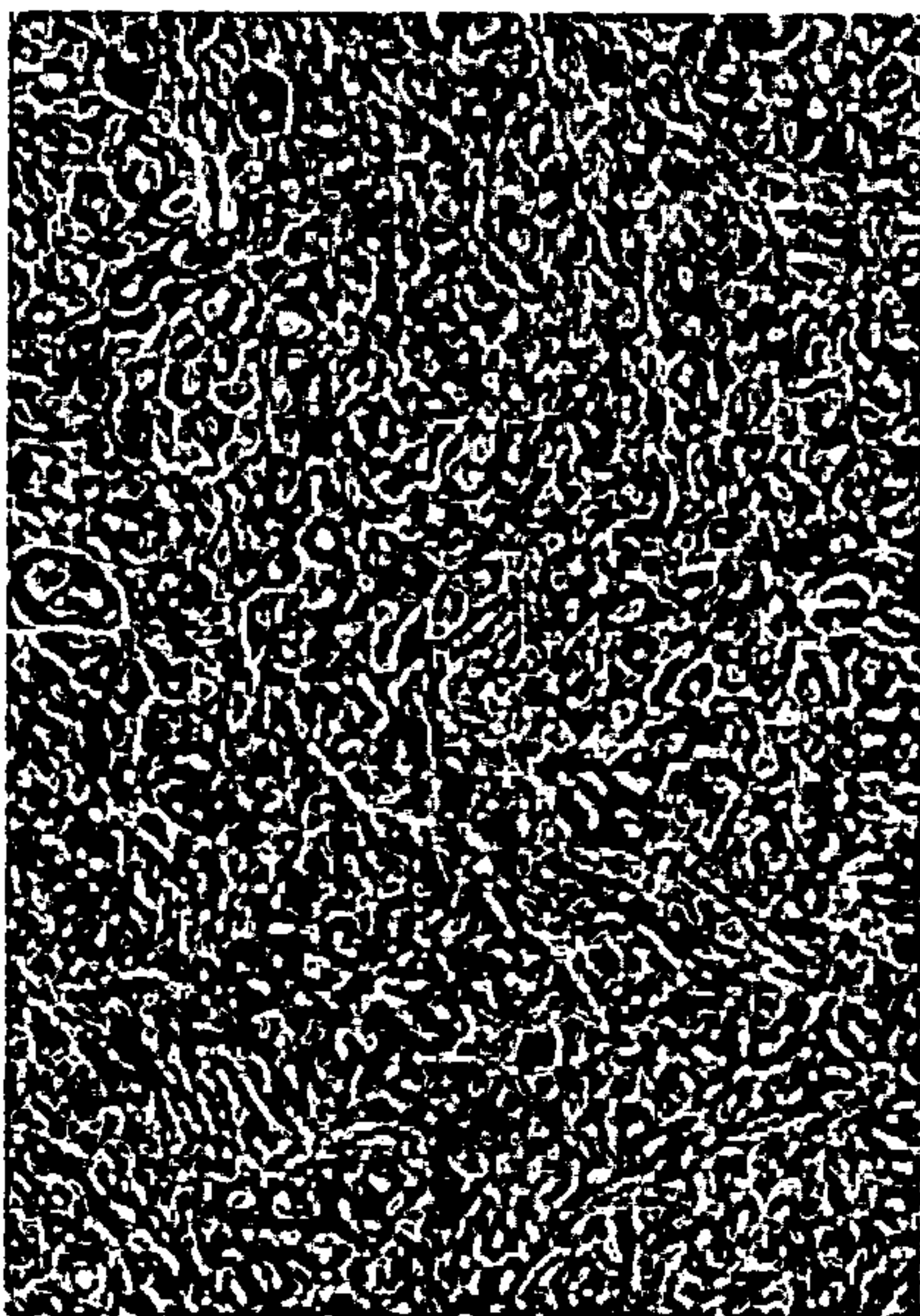
Figure 9

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Tumor treated With
PT NPX/Alex555 siRNA

Untreated

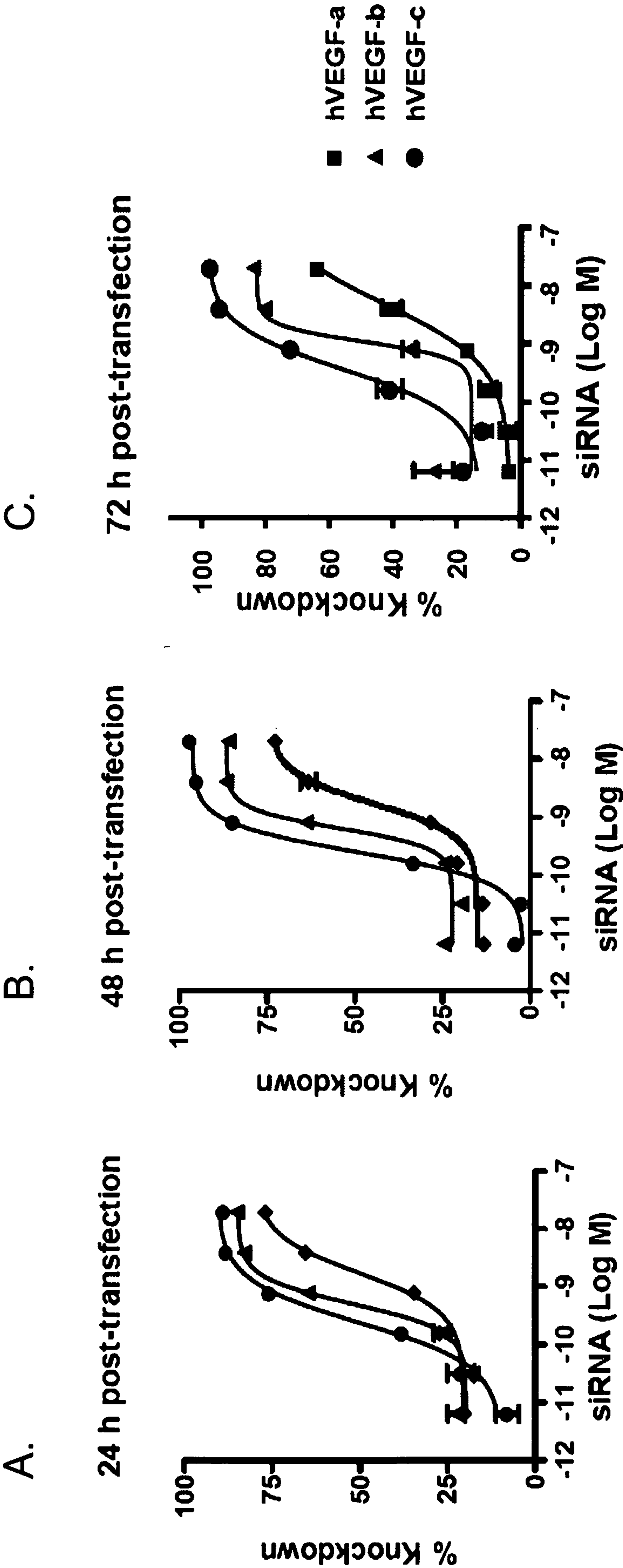


Bright Field

Fluorescent

Overlapping

Figure 10



siRNA	24 h post-transfection IC ₅₀ (nM)	48 h post-transfection IC ₅₀ (nM)	72 h post-transfection IC ₅₀ (nM)
hVEGF -a	1.76 ± 0.047	1.65 ± 0.055	4.77 ± 0.21
hVEGF -b	0.52 ± 0.032	0.63 ± 0.021	1.07 ± 0.15
hVEGF -c	0.24 ± 0.055	0.24 ± 0.019	0.35 ± 0.06

Figure 11

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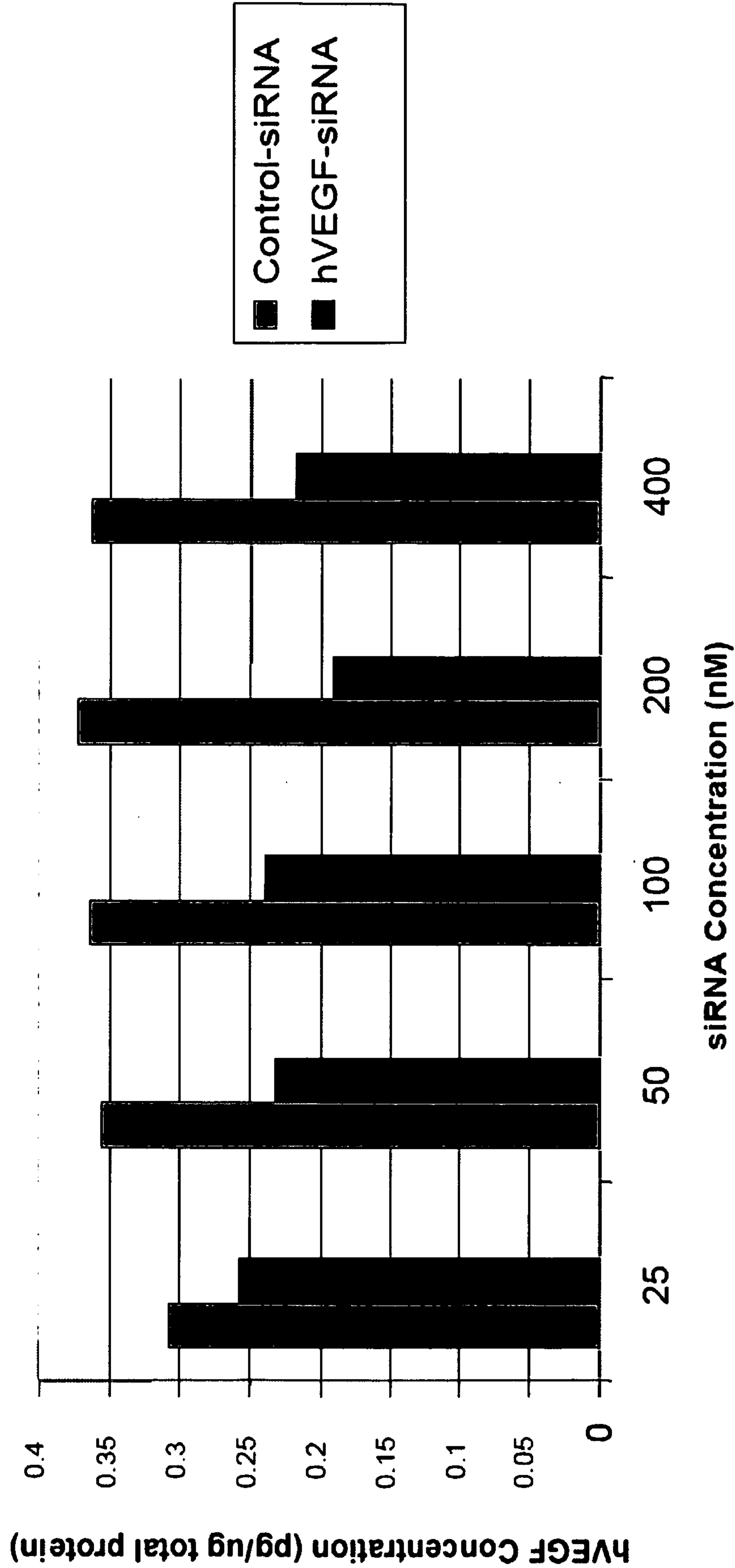


Figure 12

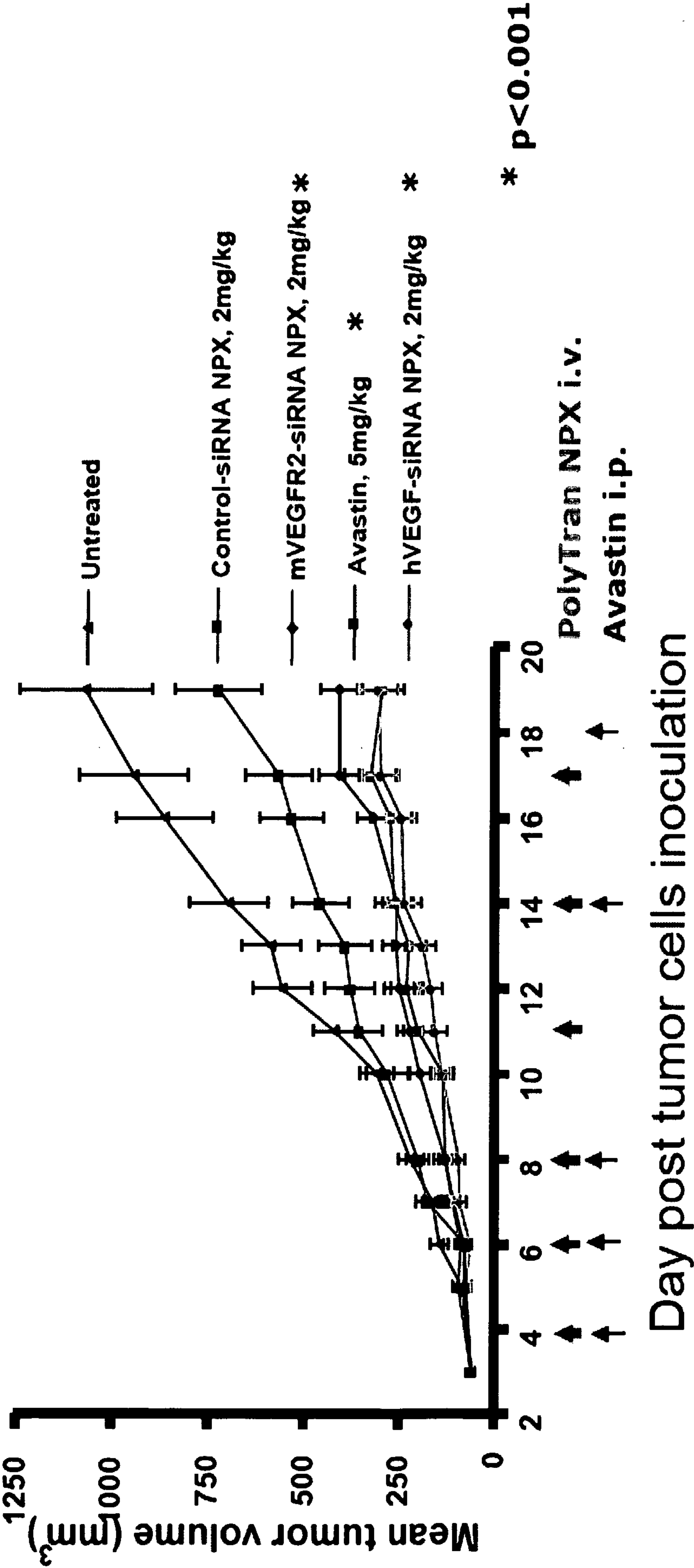


Figure 13

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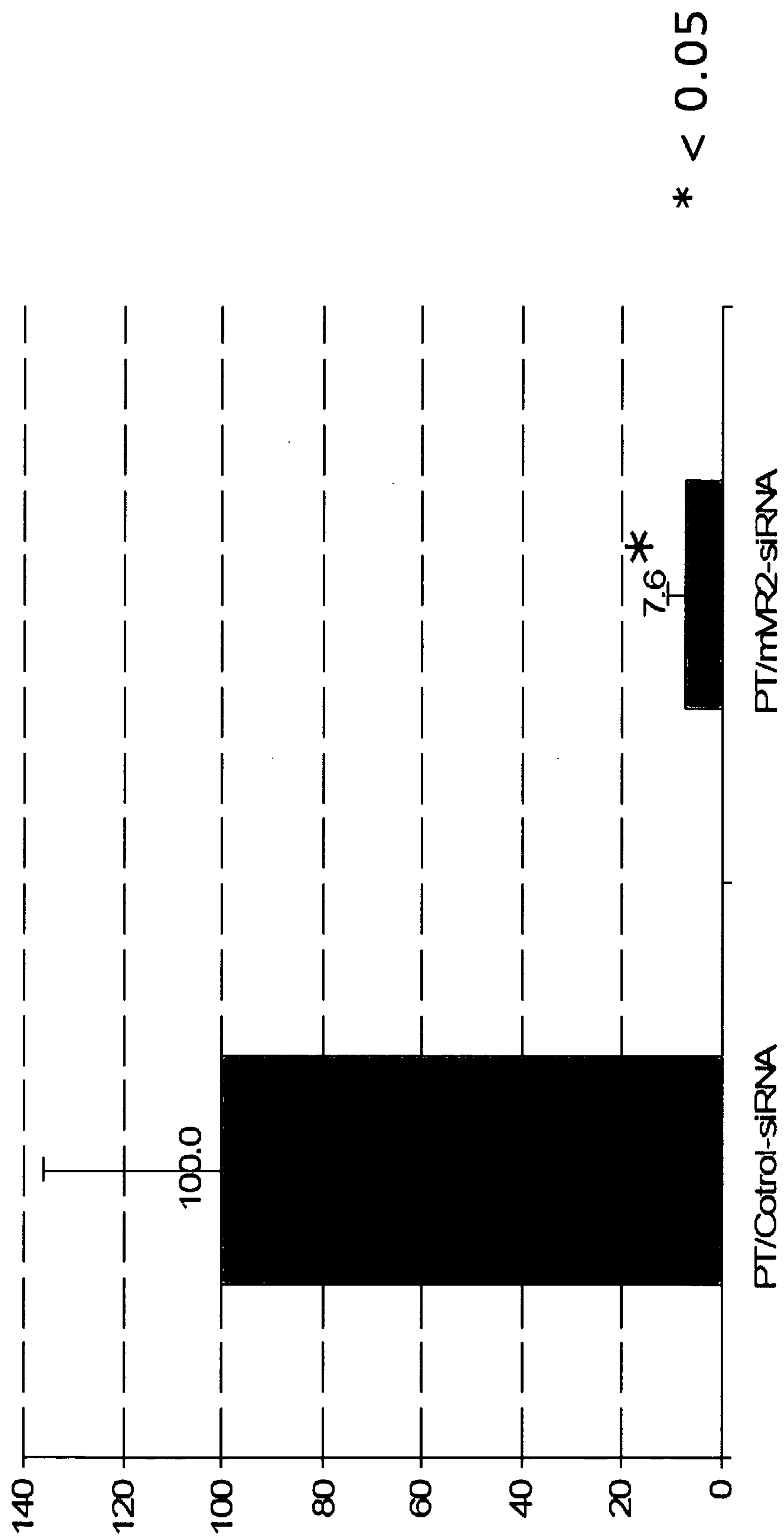


Figure 14