|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | | | **How to get** | **Status** |
| Geometry | Adipocyte | Diameter of one cell | Search | O |
| Surface area of one cell | Calculate | - |
| Volume of one cell | Calculate | - |
| Total surface areas of adipocytes | Calculate | - |
| The number of adipocytes | Search | O |
| Capillary | Cross-sectional area of one microvessel | Search | O |
| Perimeter of one microvessel | Search | O |
| Outer diameter of one microvessel | Calculate | - |
| Capillary-adipocyte ratio | Search | O |
| Capillary density | Search | O |
| Total surface area of microvessels | Calculate | - |
| Endothelial cell thickness | Search | O |
| Surface areas of one endothelial cell | Search | Δ |
| Total blood volume | Search | X |
| Interstitial space | Capillary basement membrane (CBM) thickness | Search | Δ |
| Adipocyte basement membrane (ABM) thickness | Search | Δ |
| Extracellular fluid or interstitial fluid volume fraction | Search | O |
| Non-fluid components volume fraction in CBM | Search | O |
| Non-fluid components volume fraction in ABM | Search | O |
| Non-fluid components volume fraction in extracellular matrix (ECM) | Search | O |
| Size of pore in CBM | Search | Δ |
| Size of pore in ABM | Search | Δ |
| Kinetics | VEGF-A | VEGF-A binding to VEGFR1 | Check cited literature | O |
| VEGF-A binding to VEGFR2 | Check cited literature | O |
| VEGF-A binding to NRP1 | Check cited literature | O |
| VEGF-A binding to NRP2 | Check cited literature | O |
| VEGF-A binding to GAGs | Check cited literature | O |
| VEGF-B | VEGF-B binding to VEGFR1 | Search | O |
| VEGF-B binding to NRP1 | Search | O |
| VEGF-B binding to GAGs | Search | O |
| Receptors | Coupling of NRP1 and VEGFR1 | Check cited literature | O |
| Coupling of NRP1/2 and VEGFR2 | Check cited literature | Δ |
| VEGFR internalization | Check cited literature | O |
| Binding site densities | | ECM | Check cited literature | X |
| CBM | Check cited literature | X |
| ABM | Check cited literature | X |
| Transport | | VEGF-165 secretion rate | Tuned | X |
| VEGF-121 secretion rate | Tuned | X |
| VEGF-B secretion rate | Tuned | X |
| VEGF clearance | Check cited literature | O |
| VEGF degradation | Check cited literature | O |

* **Adipocyte size (mean diameter)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Strain** | **Sex** | **n** | **Age** | **Diet** | **Duration of diet** | **Body weight** | **Location** | **Method** | **Value** |
| (Lijnen et al., 2006) | Mouse | Swiss × 129SV | Male | 15 | 20 wk. | SFD | 15 wk. | 38±1.4 g | Gonadal fat | Computer-assisted image analysis | 44.99 µm  [42.37, 47.47] |
| Male | 10 | HFD | 57±1.4 g | 65.80 µm  [63.93, 67.61] |
| (Lijnen et al., 2001) | Mouse | C57/Bl6 × 129SVj | Both | ? | 22 wk. | SFD | 17 wk. | 27±2.2 g | Gonadal fat | Computer-assisted image analysis | 49±4.2 µm |
| Both | ? | HFD | 39±3.1 g | 80±5.3 µm |
| (Maquoi et al., 2002) | Mouse | C57/Bl6 × 129SVj | Male | 2 | 20 wk. | SFD | 15 wk. | 28±1.2 g | Gonadal fat | Computer-assisted image analysis | 42 µm |
| Male | 6 | HFD | 40±1.4 g | 83±3 µm |
| (Morange et al., 2000) | Mouse | C57BL/6 × 129SV | Both | 7 to 11 | 21 wk. | SFD | 17 wk. | 28±1.4 g | Gonadal fat | Computer-assisted image analysis | 49±4.3 µm |
| Both | 7 to 11 | HFD | 42±2 g | 82±3.5 µm |
| (Voros et al., 2005) | Mouse | C57Bl/6 | Male | ? | 20 wk. | SFD | 15 wk. | 30.0±0.62 g | Gonadal fat | Computer-assisted image analysis | 28.77 µm  [27.69, 29.81] |
| Male | ? | HFD | 46.3±1.77 g | 52.93 µm  [52.47, 53.38] |
| (Lijnen, Maquoi, et al., 2003) | Mouse | C57/Bl6 | Male | 12 to 20 | 20 wk. | SFD | 15 wk. | 33±0.91 g | Gonadal fat | Computer-assisted image analysis | 62±4.1 µm |
| Male | 12 to 20 | HFD | 45±1.4 g | 85±2.3 µm |
| (Lijnen, Demeulemeester, et al., 2003) | Mouse | C57Bl/6 × 129 SvJae | Male | 4 | 20 wk. | SFD | 15 wk. | 29.4±0.6 g | Gonadal fat | Computer-assisted image analysis | 40.05±0.76 µm |
| Male | 10 | HFD | 41±1.8 g | 94.61±4.58 µm |
| (Maquoi et al., 2003) | Mouse | B10.RIII | Male | 11 | 20 wk. | HFD | 15 wk. | 41±1.6 g | Gonadal fat | Computer-assisted image analysis | 76.36±2.25 µm |
| (Lijnen et al., 2007) | Mouse | C57Bl/6 | Male | 8 | 20 wk. | HFD | 15 wk. | 42±1.4 g | Gonadal fat | Computer-assisted image analysis | 89.13±1.46 µm |
| (Van Hul et al., 2012) | Mouse | C57Bl6/129SvJ/EMS + Ter | Male | 10 to 14 | 20 wk. | SFD | 15 wk. | 23±0.46 g | Gonadal fat | Computer-assisted image analysis | 42.4±1.95 µm |
| 10 to 14 | HFD | 27±0.72 g | 58.37±2.22 µm |

\* [,] shows minimum and maximum value.

* **The number of adipocytes**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Strain** | **Sex** | **n** | **Age** | **Diet** | **Duration of diet** | **Body weight** | **Location** | **Method** | **Value** |
| (Lijnen et al., 2001) | Mouse | C57/Bl6 × 129SVj | Both | ? | 22 wk. | SFD | 17 wk. | 27±2.2 g | Gonadal fat | Computer-assisted image analysis |  |
| Both | ? | HFD | 39±3.1 g |  |
| (Morange et al., 2000) | Mouse | C57BL/6 × 129SV | Both | 7 to 11 | 21 wk. | SFD | 17 wk. | 28±1.4 g | Gonadal fat | Computer-assisted image analysis |  |
| Both | 7 to 11 | HFD | 42±2 g |  |
| (Lijnen, Maquoi, et al., 2003) | Mouse | C57/Bl6 | Male | 12 to 20 | 20 wk. | SFD | 15 wk. | 33±0.91 g | Gonadal fat | Computer-assisted image analysis |  |
| Male | 12 to 20 | HFD | 45±1.4 g |  |

* **Blood vessel size (cross-sectional area)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Strain** | **Sex** | **n** | **Age** | **Diet** | **Duration of diet** | **Body weight** | **Location** | **Method** | **Value** |
| (Lijnen et al., 2006) | Mouse | Swiss × 129SV | Male | 15 | 20 wk. | SFD | 15 wk. | 38±1.4 g | Gonadal fat | Computer-assisted image analysis | 27±1.7 |
| Male | 10 | HFD | 57±1.4 g | 41±3.1 |
| (Voros et al., 2005) | Mouse | C57Bl/6 | Male | ? | 20 wk. | SFD | 15 wk. | 30.0±0.62 g | Gonadal fat | Computer-assisted image analysis | 49±3.4 |
| Male | ? | HFD | 46.3±1.77 g | 54±3.3 |
| (Lijnen, Maquoi, et al., 2003) | Mouse | C57/Bl6 | Male | 5 to 10 | 20 wk. | SFD | 15 wk. | 33±0.91 g | Gonadal fat | Computer-assisted image analysis | 74±4.8 |
| Male | 5 to 10 | HFD | 45±1.4 g | 140±19 |
| (Lijnen, Demeulemeester, et al., 2003) | Mouse | C57Bl/6 × 129 SvJae | Male | 4 | 20 wk. | SFD | 15 wk. | 29.4±0.6 g | Gonadal fat | Computer-assisted image analysis | ? |
| Male | 10 | HFD | 41±1.8 g | 47±2.6 |
| (Maquoi et al., 2003) | Mouse | B10.RIII | Male | 7 to 11 | 20 wk. | HFD | 15 wk. | 41±1.6 g | Gonadal fat | Computer-assisted image analysis | 76±3.9 |
| (Lijnen et al., 2007) | Mouse | C57Bl/6 | Male | 8 | 20 wk. | HFD | 15 wk. | 42±1.4 g | Gonadal fat | Computer-assisted image analysis | 108±7.7 |
| (Van Hul et al., 2012) | Mouse | C57Bl6/129SvJ/EMS + Ter | Male | 10 to 14 | 20 wk. | SFD | 15 wk. | 23±0.46 g | Gonadal fat | Computer-assisted image analysis | 59±5.1 |
| 10 to 14 | HFD | 27±0.72 g | 49±2.8 |

* **Blood vessel density (cross-sectional area)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Strain** | **Sex** | **n** | **Age** | **Diet** | **Duration of diet** | **Body weight** | **Location** | **Method** | **Value** |
| (Lijnen et al., 2006) | Mouse | Swiss × 129SV | Male | 15 | 20 wk. | SFD | 15 wk. | 38±1.4 g | Gonadal fat | Computer-assisted image analysis | 370±30 |
| Male | 10 | HFD | 57±1.4 g | 290±23 |
| (Voros et al., 2005) | Mouse | C57Bl/6 | Male | ? | 20 wk. | SFD | 15 wk. | 30.0±0.62 g | Gonadal fat | Computer-assisted image analysis | 790±41 |
| Male | ? | HFD | 46.3±1.77 g | 490±19 |
| (Lijnen, Maquoi, et al., 2003) | Mouse | C57/Bl6 | Male | 5 to 10 | 20 wk. | SFD | 15 wk. | 33±0.91 g | Gonadal fat | Computer-assisted image analysis | 280±56 |
| Male | 5 to 10 | HFD | 45±1.4 g | 200±34 |
| (Lijnen, Demeulemeester, et al., 2003) | Mouse | C57Bl/6 × 129 SvJae | Male | 4 | 20 wk. | SFD | 15 wk. | 29.4±0.6 g | Gonadal fat | Computer-assisted image analysis | ? |
| Male | 10 | HFD | 41±1.8 g | 120±6.2 |
| (Maquoi et al., 2003) | Mouse | B10.RIII | Male | 7 to 11 | 20 wk. | HFD | 15 wk. | 41±1.6 g | Gonadal fat | Computer-assisted image analysis | 210±17 |
| (Lijnen et al., 2007) | Mouse | C57Bl/6 | Male | 8 | 20 wk. | HFD | 15 wk. | 42±1.4 g | Gonadal fat | Computer-assisted image analysis | 238±16 |
| (Van Hul et al., 2012) | Mouse | C57Bl6/129SvJ/EMS + Ter | Male | 10 to 14 | 20 wk. | SFD | 15 wk. | 23±0.46 g | Gonadal fat | Computer-assisted image analysis | 740±96 |
| 10 to 14 | HFD | 27±0.72 g | 400±55 |

* **Capillary wall thickness**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Sex** | **Age** | **Diet** | **Duration of diet** | **Body weight** | **Location** | | **Method** | **Value** |
| (Simionescu et al., 1978) | Mouse | Male | ? | SFD | 7 or 10 days | 20-30 g | Bipolar microvascular fields in diaphragm | Middle segment of capillaries | Measure attenuated part of endothelial cell | 0.25±0.05 µm |
| Venular segment of capillaries | 0.17±0.07 µm |
| (Ahrendt et al., 2020) | Mouse | Male | 35 wk. | SFD | 30 wk. | 30-45 g | Lung | | Endothelial cell thickness (Stereology; photo + line grids + # of points) | 0.18 µm (approx.) |
| HFD | 50-55 g | 0.28 µm (approx.) |
| (van den Berg et al., 2003) | Rat | Male | ? | - | - | 250-350 g | Myocardial capillaries | | = (Outer capillary diameter) – (inner capillary diameter) | 0.18±0.04 µm |
| (Lash et al., 1989) | Zucker rat | Male | 11 wk. | Lean | 6 wk. (ad libtum) | ? | Plantar muscle | | Endothelial thickness  (photo) | 0.174±0.004 µm |
| Genetic obesity | 6 wk. (ad libtum) | 0.203±0.007 µm |
| 18 wk. | Lean | 13 wk. (ad libtum) | 0.147±0.005 µm |
| Genetic obesity | 13 wk. (ad libtum) | 0.136±0.004 µm |
| (Cinti, 2018) | Rat |  | ?  (young) | ? | ? | ? | Epididymal adipose tissue | | Attenuated part of endothelial cell (measured by YLee) | >0.2 µm (approx.) |

* **Capillary basement membrane (CBM) thickness**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Age** | **n** | **Status** | **Body weight** | **Location** | **Method** | **Value** |
| (Cuthbertson & Mandel, 1986) | Mouse | 4 mo. | 4 | ? | ? | Retina | Microscope (photo)  (thickness) = (CBM area)  /(circumference) | 59±13 nm |
| 20 mo. | 4 | 154±27 nm |
| (Rodrigues et al., 1983) | Mouse | 6 mo. | ? | Normal  (Uninfected) | ? | Retina | Transmission electron microscopy (TEM) | 69±5.5 nm |
| 8 | Diabetes  (EMC virus infected) | 91±10.2 nm |
| (Ceafalan et al., 2019) | Mouse | 6 mo. | 100 | Normal | ? | Brain | Transmission electron microscopy (TEM) | 56.78±12.50 nm |
| (Creutzfeldt et al., 1970) | Spiny mouse | 220±146 days | 8 | Normal | 45±10 g | Gastrocnemius (muscle) | Microscope (photo) | 73±16 nm |
| 207±125 days | 6 | Severely impaired glucose tolerance | 50±11 g | 80±18 nm |
| 462±174 days | 5 | Diabetes | ? | 105±9 nm |
| (Carlson et al., 2003) | Mouse | 300-350 days | 8 | Lean | 39.40±3.11 g | Retina | Transmission electron microscopy (TEM) morphometry  (Intersection of CBM with sampling grid lines) | 92.87±18.90 nm |
| 14 | Genetic diabetes | 40.52±3.16 g | 113.09±9.57 nm |
| 10 | Lean | 39.40±3.11 g | Extensor digitorum  (muscle) | Transmission electron microscopy (TEM) morphometry  (Intersection of CBM with sampling grid lines) | 76.75±14.17 nm |
| 8 | Genetic diabetes | 40.52±3.16 g | 72.10±16.85 nm |
| (Lash et al., 1989) | Zucker rat | 11 wk. | 6 | Lean (FA/fa) | ? | Plantar muscle | Microscope (photo)  (thickness) = (CBM area)  /(circumference) | 62±6.64 nm |
| 6 | Genetic obesity (fa/fa) | 68±12.1 nm |
| 18 wk. | 6 | Lean (Fa/fa) | 56±7.32 nm |
| 7 | Genetic obesity (fa/fa) | 58±6.57 nm |
| (Fraselle-Jacobs et al., 1987) | Rat | 6 mo. |  | Normal | 250-500 g  (Mean: 350g) | Epididymal adipose tissue | Electron microscope morphometry | [98.28−145.17 nm](geometric/capillary%20basement%20membrane/Screen%20Shot%202022-12-15%20at%2011.31.59%20AM.tif) |
| (Danis & Yang, 1993) | Zucker rat | 6-7 mo. |  | Lean (Fa/fa) | ? | Retina | Transmission electron microscopy (TEM) | 89.0 nm |
|  | Genetic obesity & diabetes (fa/fa) | 113.4 nm |
| (Belligoli et al., 2019) | Human | 48±12 y |  | Lean | ? | Visceral adipose tissue | Transmission electron microscopy (TEM) | 103.38 nm  [67.23, 194.26] |
| 41±9 y |  | Obese without diabetes | 108.78 nm  [60.47, 181.76] |
| 52±9 y |  | Obese with type 2 diabetes | 139.87 nm  [68.24, 209.12] |

* **~~Adipocyte~~ basement membrane (ABM) thickness**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Age** | **Status** | **Body weight** | **Location** | **Method** | **Value** |
| (Fraselle-Jacobs et al., 1987) | Rat | 6 mo. | Normal | 250-500 g  (Mean: 350g) | Epididymal adipose tissue | Electron microscope morphometry | nm |
| (Comley & Fleck, 2010) | Porcine | ? | ? | ? | Dermis adipose tissue | Scanning electron microscope & laser confocal microscope  (Reinforced basement membrane) |  |
| (Abrahamson, 1986) | ? | ? | ? | ? | ? | ? | 100 nm |
| (Marilyn G. Farquhar, 1978) | ? | ? | ? | ? | ? | ? | 20 – 50 nm |
| (Farquhar & Palade, 1965) | Toad | Adult | ? | ? | Skin epidermis | Light microscopy | < 30 nm |
| < 50 nm |

**A picture containing mirror, hand glass, bowed instrument

Description automatically generated**

Basement membrane

= lamina lucida

+ lamina densa (basal lamina)

+ reticular lamina

**(Fraselle-Jacobs *et al*., 1987)**

* **Pore size in basement membrane (diameter)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Age** | **Status** | **Body weight** | **Location** | **Method** | **Value** |
| (Antonio Martinez-Hernandez, 1978) | Mouse | ? | ? | ? | Kidney  (Glomerular BM) | Routine electronic microscopy |  |
| Parietal  yolk sac carcinoma  (Neoplastic basement membrane) |
| (Sarin, 2010) | ? | ? | ? | ? | Capillary in adipose tissue | ? | < 5 nm |
| (Carpita et al., 1979) | Plants | ? | ? | ? | Hair cells/palisade parenchyma cells  (Cell wall; Semi-dehydrated ECM) | Phase-contrast microscopy | 7 – 10.4 nm |

* **Pore size in extracellular matrix in adipose tissue (diameter)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Age** | **Status** | **Body weight** | **Location** | **Method** | **Value** |
| (Song et al., 2018) | Human | 20-40 yr | Healthy | ? | Decellularized human adipose tissue-derived ECM scaffolds extracted from abdomen | Scanning electron microscopy | 20–200µm |

* **Endothelial cell area**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Age** | **Diet** | **Body weight** | **Location** | **Method** | **Value** |
| (Haas & Duling, 1997) | Golden hamster | ? | ? | ? | Cheek pouch **arterioles** | Bright-field video microscopy | 945.2−1029.6 |
| (Behndig et al., 2001) | Mouse | 4 mo. | ? | ? | Central corneal endothelium | Light microscopy | 365.36  [320, 425.71] |
| (Behndig, 2008) | Mouse | 10.4±3.0 mo. | ? | ? | Central corneal endothelium | Light microscopy | 246±35 |
| (Ahrendt et al., 2020) | Mouse | 35 wk. | SFD | 30-45 g | Lung | Surface area of endothelial cells facing the capillary lumen  (Stereology; photo + line grids + # of points) | 150−250 (approx.) |
| HFD | 50-55 g | 150−290 (approx.) |

\* [,] shows minimum and maximum value.

* **Interstitial/extracellular fluid volume fraction**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Sex** | **Age** | **Diet** | **Body weight** | **Location** | **Method** | **Inter/extra** | **Value** |
| (Eigenmann et al., 2017) | Mouse | Both | 8-12 wk. | ad libitum | 19-34 g (mean: 23 g) | Adipose | 1. Get extracellular volume fraction using 51Cr-EDTA injection 2. Get residual plasma space by 125I-HAS injection 3. Get interstitial volume fraction by: (Int. vol. frac.) = (Ext. vol. frac.) – (Res. pl. vol. frac.) | Extracellular | 0.101  in ml/g tissue |
| Interstitial | 0.093  in ml/g tissue |
| (Digirolamo & Owens, 1976) | Wistar rat | Male | 1.2-16 mo. | ad libitum | 110-750 g | Epididymal fat | 1. Extract lipid and determine triglyceride and defatted dry residue (DDR). (tissue water) = (tissue wet weight) – (weight of lipid) – (DDR) 2. ??? (intracellular water) = (tissue water) – (extracellular water) | Outside of adipocytes | 0.160 in ml/g tissue |

* **VEGF165:VEGFR1 binding affinity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **Receptor** | **Method** | **Ligand/receptor source** | **()** | **()** |  |
| (Yen et al., 2011) |  |  |  |  |  |  | 33 pM |
| (Waltenberger et al., 1994) | Recombinant 125I-VEGF165 expressed in baculovirus system | Human VEGFR1 on PAE cells or HUVECs | Radioligand  (Scatchard analysis) | Porcine aortic endothelial **(PAE) cells** transfected with a VEGFR1-expressing vector | ? | ? | 16 pM |
| **HUVECs** | 9 pM |
| (Mamer et al., 2020) | Recombinant VEGF165  **(10, 20, 40nM)** | Immobilized recombinant VEGFR1 protein | SPR | Obtained from R&D Systems |  |  | pM |
| (Teran & Nugent, 2019) | Recombinant VEGF165 | Immobilized VEGFR1 Fc\* chimera | SPR | Obtained from R&D Systems |  |  | pM |
| (von Tiedemann & Bilitewski, 2002) | VEGF165  (Recombinant Pichia pastoris strain) | Immobilized sVEGFR1 | SPR | Sf158 insect cells infected with a baculovirus-based vector (both ligand and receptor) |  |  | pM |

\* Fc: pre-dimerized

* **VEGF165:VEGFR2 binding affinity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **Receptor** | **Method** | **Ligand/receptor source** | **()** | **()** |  |
| (Yen et al., 2011) |  |  |  |  |  |  | 100 pM |
| (Huang et al., 1998) | Recombinant VEGF165  (**50 nM**) | Recombinant sVEGFR2  (Full length **mouse** Flk-1 cDNA) | SPR | Spodoptera frugiperda (Sf9) infected with sVEGFR2 recombinant baculovirus |  |  | 340 pM |
| Recombinant VEGF165  (**5 nM**) |  |  | 110 pM |
| Recombinant **VEGF164**  (**20 nM**) |  |  | 330 pM |
| Recombinant **VEGF164**  (**5 nM**) |  |  | 140 pM |
| (Whitaker et al., 2001) | Carrier-free recombinant VEGF165 | Human VEGFR2 on COS-1 cells | Radioligand  (Saturation analysis) | COS-1 cells transiently transfected with human VEGFR2 cDNA | ? | ? | 339 pM |
| (Waltenberger et al., 1994) | Recombinant 125I-VEGF165 expressed in baculovirus system | Human VEGFR2 on PAE cells or HUVECs | Radioligand  (Scatchard analysis) | Porcine aortic endothelial **(PAE) cells** transfected with a VEGFR2-expressing vector | ? | ? | 760 pM |
| **HUVECs** | 770 pM |
| (Cunningham et al., 1999) | VEGF165  (**0.625, 1.25,**  **2.5, 5 nM**) | Recombinant VEGFR2 Fc\* | SPR | SF21 cells expressing VEGFR2 Fc or cbu |  |  | pM |
| VEGF165  (**1.14, 2.28,**  **4.55, 6.83 nM**) | Recombinant VEGFR2 cbu† |  |  | pM |
| (Mamer et al., 2020) | Recombinant VEGF165  (**10, 20, 40nM**) | Immobilized recombinant VEGFR2 protein | SPR | Obtained from R&D Systems |  |  | pM |
| (Teran & Nugent, 2019) | Recombinant VEGF165 | Immobilized VEGFR2 Fc\* chimera | SPR | Obtained from R&D Systems |  |  | nM |

\* Fc: pre-dimerized fusion protein

† cbu: monomeric fusion protein

* **VEGF165:NRP1 binding affinity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **Receptor** | **Method** | **Ligand/receptor source** | **()** | **()** |  |
| (Yen et al., 2011) |  |  |  |  |  |  | 312 pM |
| (Whitaker et al., 2001) | Carrier-free recombinant VEGF165 | Human NRP1 | Radioligand  (Saturation analysis) | COS-1 cells transiently transfected with human NRP1 cDNA | ? | ? | 2.09 nM |
| (Soker et al., 1996) | Recombinant 125I-VEGF165 | NPR1 on HUVEC | Radioligand  (Scatchard analysis) | **VEGF-165**  Sf-9 insect cells infected with a baculovirus-based vector expressing VEGF-165 cDNA | ? | ? | 200 pM |
| NRP1 on breast cancer cell  (MDA-MB-231) | 280 pM |
| (Soker et al., 1998) | Recombinant 125I-VEGF165 | NRP1 on porcine aortic endothelial (PAE) cells | Radioligand  (Scatchard analysis) | **VEGF-165**  Sf-21 insect cells infected with recombinant baculovirus vectors  **NRP1**  PAE cells transfected with NRP1 cDNA | ? | ? | 320 pM |
| (Fuh et al., 2000) | Biotinylated VEGF165 | First 600 amino acids of **mouse** NPR-1 extracellular domain (ECD), which lacked C-terminal MAM domain (immobilized) | **SPR**  Low density  (350 RU) | **NRP1**  Transfected D. melanogaster cells |  |  | 2,000 nM |
| **SPR**  High density  (1400 RU) | 113 nM |
| **ELISA**  No heparin | 120 nM |
| **ELISA**  Add heparin | 25 nM |
| (Pan et al., 2007) | VEGF165 | Human sNRP1-Fc†   * Immobilized * Containing ECD * Without MAM domain | SPR  (Steady-state analysis) | **VEGF165**  Purchased from R&D Systems  **sNRP1**  Transfected Chinese hamster ovary cells | ? | ? | 120 nM |
| (Teran & Nugent, 2019) | Recombinant VEGF165 | Immobilized **rat** NRP-1 Fc\* chimera | SPR | Obtained from R&D Systems |  |  | nM |
| Immobilized **mouse** sNRP-1 monomer (only ECD of the mouse sequence) |  |  | nM |

\* Fc: pre-dimerized

†Fc: sNRP1s constructs were cloned into the expression vector pRK5 either fused to the Fc portion of human IgG1 to facilitate affinity purification.

* **VEGF165:NRP2 binding affinity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **Receptor** | **Method** | **Ligand/receptor source** | **()** | **()** |  |
| (Finley et al., 2011) |  |  |  |  |  |  | 1 nM |
| (Geretti et al., 2007) | 125I-VEGF165 | NRP2 expressed from PAE cells | Radioligand  (Saturation analysis) | **VEGF165**  Purchased from R&D Systems or Provided by National Cancer Institute  **NRP2**  PAE cells transfected with NRP2 cDNA | ? | ? |  |
| (Gluzman-Poltorak et al., 2000) | 125I-VEGF165 | Recombinant NRP2 (splice form a22) expressed from PAE cells | Radioligand  (Scatchard analysis) | **VEGF165**  SF9 cells infected with baculoviruses  **NRP2**  PAE cells co-transfected with the PECE/np-2(a17) or PECE/np-2(a22) expression vectors and the pBabePuro plasmid | ? | ? | 0.13 nM |

* **VEGF121:VEGFR1 binding affinity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **Receptor** | **Method** | **Ligand/receptor source** | **()** | **()** |  |
| (Yen et al., 2011) |  |  |  |  |  |  | 33 pM |
| (Mamer et al., 2020) | Recombinant VEGF121  **(10, 20, 40nM)** | Immobilized recombinant VEGFR1 protein | SPR | Obtained from R&D Systems |  |  | nM |
| (Teran & Nugent, 2019) | Recombinant VEGF121 | Immobilized VEGFR1 Fc\* chimera | SPR | Obtained from R&D Systems |  |  | nM |

\* Fc: pre-dimerized

* **VEGF121:VEGFR2 binding affinity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **Receptor** | **Method** | **Ligand/receptor source** | **()** | **()** |  |
| (Yen et al., 2011) |  |  |  |  |  |  | 100 pM |
| (Mamer et al., 2020) | Recombinant VEGF165  **(10, 20, 40nM)** | Immobilized recombinant VEGFR1 protein | SPR | Obtained from R&D Systems |  |  | nM |
| (Teran & Nugent, 2019) | Recombinant VEGF121 | Immobilized VEGFR2 Fc\* chimera | SPR | Obtained from R&D Systems |  |  | nM |
| (Papo et al., 2011) | VEGF121 | Immobilized recombinant VEGFR2 extracellular domain | SPR | Obtained from R&D Systems |  |  |  |

\* Fc: pre-dimerized

* **VEGF121:NRP1 binding affinity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **Receptor** | **Method** | **Ligand/receptor source** | **()** | **()** |  |
| (Pan et al., 2007) | VEGF | Human sNRP1-Fc†   * Immobilized * Containing ECD * Without MAM domain | SPR  (Steady-state analysis) | **VEGF121**  Purchased from PeproTech  **sNRP1**  Transfected Chinese hamster ovary cells | ? | ? | 220 nM |

* **VEGF-B:VEGFR1 binding affinity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **Receptor** | **Method** | **Ligand/receptor source** | **()** | **()** |  |
| (Olofsson et al., 1998) | mVEGF-B186 | VEGFR1 | Competitive binding assay  (Recombinant hVEGF-165) | High Five cells infected with mVEGF-B186 pFASTBAC1 virus, NIH 3T3/VEGFR1 cells | ? | ? | pM |

* **VEGF-B:NRP1 binding affinity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **Receptor** | **Method** | **Ligand/receptor source** | **()** | **()** |  |
| (Mota et al., 2022) | Immobilized  Full length VEGF-B167 | NRP1-b1 | SPR | NRP1-b1 from 2 L E.coli Rosetta | ? | ? | 36 |
| VEGF-B167 peptide | Immobilized NRP1-b1 |  |  | 0.39 |
| VEGF-B186 peptide |  |  | 9.55 |

* **VEGFR1:NRP1 binding affinity (Coupling rate)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **VEGFR1** | **NRP1** | **Method** | **VEGFR1 source** | **NRP1 Source** |  | **()** |  |
| (Yen et al., 2011) |  |  |  |  |  |  |  |  |
| (Fuh et al., 2000) | VEGFR1 extracellular domain | NRP1 extracellular domain | ELISA or SPR | Chinese hamster ovary (CHO) cells | Transfected *D. melanogaster* cells |  |  | 1.8 nM |

* **VEGFR2:NRP1 binding affinity (Coupling rate)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Protein** | **Method** | **Source** |  | **()** |  |
| (Yen et al., 2011) | VEGFR2:NRP1 |  |  |  |  | - |
| Mac Gabhann, 2005  (mac Gabhann & Popel, 2005) | VEGFR2:NRP1 | Calculate the diffusion-limited rate and set it as the coupling rate |  |  |  | - |
| (Whitaker et al., 2001) | Human VEGFR2:NRP1 | Competition binding assay | COS-1 cell transfected with either VEGFR2 or NRP1 cDNAs, or both |  |  |  |
| (Dembo et al., 1982) | [IgE2:Fc]:Fc  (IgE2: dimerized IgE) | Calculate from   1. : Rate constant of crosslinking 2. : Experimentally determined (estimated by fitting ODE to histamine release level (%)) 3. : Initial number of free Fc receptors per cell (measured) 4. : Surface area of the basophil (Dembo *et al.*, 1979a) | **IgE**  Human IgE myeloma protein  **Fc receptors**  Human basophils |  | ? | - |

* **Protein-protein dimerization rate**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Protein** | **Method** | **Source** |  | **()** |  |
| (Mamer et al., 2019) | Arbitrary receptors | Assumed  (ODE system) | - |  |  | - |
| (Dijkman et al., 2018) | Rat NTS1† mutant fluorescently labelled at the intracellular end of TM4  (Cy3 and Cy5) | Single-molecule Förster resonance energy transfer (smFRET) | Expressed in *E. coli* BL21 as a fusion construct NTS1BH6‡ | () | 0.575 | - |
| (Moore et al., 1999) | Recombinant humanized  anti-VEGF | Dissociation experiment  (Fit to the plot of the concentration of dimer vs. time) | Purified from Chinese hamster ovarian cells |  |  | 0.91–350 µM |
| (M. J. Chen & Mayo, 1991) | Human Platelet factor 4 (PF4) | Saturation-transfer 1H Nuclear Magnetic Resonance (ST H NMR)  & Spin-Lattice Relaxation | Outdated human platelet |  |  | 147–500 µM |
| (Patapoff et al., 1993) | Recombinant human growth hormone (hGH) | Size exclusion high-performance liquid chromatography | Lyophilized recombinant hGH obtained from Genentech, Inc. |  |  | 2.6 µM |
| (Darke et al., 1994) | HIV-1 protease | Fit to the fluorescence change of an active-site-directed fluorescent probe upon its binding to HIV-1 protease | Expressed in *Escherichia coli* |  | 0.025 |  |

† Class A GPCR neurotensin receptor 1

‡ NTS1 is truncated at the N-terminus (1–42), has a hexa-His- tag added to its C-terminus, and is flanked by TEV protease recognition sites separating it from its N- and C-terminal fusion partners, maltose binding protein and thioredoxin, respectively, followed by an additional C-terminal deca-His-tag.

* **VEGFR internalization**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Receptor status** | **Data source** | **Data** | **Model** | **Method** | **Receptors** | **Value** |
| (mac Gabhann & Popel, 2004) | Constitutive (free) | Wang, 2002 | The time courses of 125I-labeled VEGF internalization  (% 125I-VEGF bound on cell surface) | PDE for binding of VEGF and PlGF to VEGFR1/2 on endothelial cells | Apply a simplified version of the PDE model for a single growth factor and single receptor population to data | Either VEGFR1 or VEGFR2 | (assumption) |
| Bound |  |
| (Tan et al., 2013a) | Constitutive (free) | * (Lamalice *et al*., 2006) * (Chabot *et al*., 2009) * (Schneeweis *et al.*, 2010) * (Bruns *et al*., 2010) * (Zhang *et al*., 2010) | The time courses of   * # and normalized phosphorylated VEGFR2 * # and normalized phosphorylated Akt | ODE for Gab1/2-dependent VEGFR2 pathway to Akt activation | Estimate internalization rate | VEGFR2 |  |
| Bound |  |
| (Tan et al., 2013b) | Constitutive (free) | * (Lamalice *et al*., 2006) * (Chabot *et al*., 2009) * (Bruns *et al*., 2010) * (Zhang *et al*., 2010) | The time courses of   * # and normalized phosphorylated VEGFR2 * # and normalized phosphorylated Akt | ODE for VEGFR2 pathway to ERK activation | Estimate internalization rate | VEGFR2 |  |
| Bound |  |
| (Weddell & Imoukhuede, 2017) | Unphosphorylated | * **ICAM-1**:   Muro *et al.*, 2003  Muro *et al.*, 2004   * **VEGFR2**: Lampugnani *et al.*, 2006 * **EGFR**:   Danglot *et al.*, 2010   * **Heparin sulfate and integrin**:   Greene *et al.*, 2012 | * % Total internalized receptors * % Total receptors localized to the nucleus * % Total receptors co-localized with early endosomes * Receptor localization with early endosomes over time * % Total receptor co-localization with late endosomes * Receptor co-localization with late endosomes over time | ODE for RTK endocytosis signaling | Estimate RTK-specific internalization rate for the receptors and get a generalized rate | * VEGFR1 * VEGFR2 * IGFR1 * FGFR1 * EFGFR * PDGFRα * PDGFRβ * Tie2 |  |
| Phosphorylated |  |
| Dissertation:  (Castleberry, 2022) | Constitutive (free) | Wang, 2002 | The time courses of 125I-labeled VEGF internalization  (% 125I-VEGF bound on cell surface) | ODE for cross-family binding interactions | Approximating a first-order reaction rate from data | VEGFR1 or VEGFR2 |  |
| Bound |  |
| (Sarabipour, 2022)  Submitted | Constitutive (free) | Experiment on HUVECs | * Whole-cell VEGF receptors expression levels in the absence of exogenous ligands * Localization patterns (cell surface vs intracellular) * Whole-cell VEGF receptors expression levels when inhibiting recycling pathways (with or without CHX) | ODE for trafficking of VEGFR1, VEGFR2, and NRP1 on HUVECs  (no nucleus) | Estimate internalization rate for VEGFR1, VEGFR2, and NRP1 based on experimental measurements | VEGFR1 |  |
| VEGFR2 |  |
| NRP1 |  |

* **VEGF:GAG binding**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Ligand** | **GAG** | **Method** | **Source** | **()** | **()** |  |
| (Yen et al., 2011) |  |  |  |  |  |  | 24 nM |
| (Filion & Popel, 2004) |  |  |  |  |  |  | 1.03 nM |
| (Nugent & Edelmant, 1992) | Recombinant basic fibroblast growth factor (bFGF) | HSPG | Radioligand  (Direct target-ligand binding;  Curve fitting to time-course for association and dissociation) | **bFGF**  From Chiron Inc.  **HSPG**  Mouse Balb/c3T3-produced extracellular matrix coated tissue (only HSPG) |  |  | 1.03 nM |
| (Lim et al., 2016) | Recombinant VEGF165a | Heparan sulfate | SPR | **VEGF165a**  Obtained from R&D Systems |  |  | 3.3 nM |

* **VEGF clearance**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Species** | **Status** | **Sex** | **Protein** | **Protein source** | **Data** | | **Method** | **Value ()** |
| (Eppler et al., 2002) | Human | Patients with coronary artery disease | Both | rhVEGF165 | ? | **Mean (SD) VEGF plasma concentration vs. time** | 17 ng/kg/min | Non-compartment model |  |
| 50 ng/kg/min | Non-compartment model |  |
| Dose-independent | Fit a mechanism-based, target-mediated drug distribution model to data |  |
| (George et al., 2015) | C57Bl/6 mice | ? | ? | VEGF121 | From ProSpec | **Mean VEGF121 plasma concentration vs. time**   1. Inject 123 nmol/kg of VEGF121 in the femoral artery. 2. Sample blood repeatedly for 4 hours. | | Fit a two-compartment pharmacokinetic model to data |  |

* **VEGF degradation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **VEGF source** | **Used cell or complex** | **Method** | **Value ()** |
| (Kleinheinz et al., 2010) | Recombinant human VEGF165 | Equine (horse) collagen complex charged with VEGF165 | 1. The complexes were charged with VEGF165 in three different complexes: 0.8 µg, 10 µg, 80 µg. 2. The complexes were incubated for 5 days. 3. VEGF dissolution in aqueous solution was analyzed repeatedly. |  |
| (R. R. Chen et al., 2007) | VEGF165 from Biological Resources Branch of the National Cancer Institute | Incubated with dermal microvascular endothelial cells (MECs) | 1. VEGF was incubated with MECs *in vitro*. 2. Measure % of total bioactivity of VEGF. 3. Calculate the half-life of VEGF based on the time required for VEGF to lose half its bioactivity. |  |
| (Serini et al., 2003) | Recombinant human VEGF165 | Human endothelial cells | 1. VEGF-A165 and 10 nCi of 125I-VEGF were incubated for different intervals of time with EC plated on Matrigel. 2. VEGF-A was immunoprecipitated from the medium with a polyclonal anti-VEGF-A antibody. 3. Radioactivity corresponding to the VEGF-A band in SDS±PAGE (12%) was counted and used to calculate the half-time by EnzFitter software |  |

**Chart, line chart

Description automatically generated**

**References**

Abrahamson, D. R. (1986). Recent studies on the structure and pathology of basement membranes. In *The Journal of Pathology* (Vol. 149, Issue 4). https://doi.org/10.1002/path.1711490402

Ahrendt, N., Steingrüber, T., Rajces, A., Lopez-Rodriguez, E., Eisenberg, T., Magnes, C., Madeo, F., Sedej, S., Schmiedl, A., Ochs, M., Mühlfeld, C., & Schipke, J. (2020). Spermidine supplementation and voluntary activity differentially affect obesity-related structural changes in the mouse lung. *American Journal of Physiology - Lung Cellular and Molecular Physiology*, *319*(2). https://doi.org/10.1152/ajplung.00423.2019

Antonio Martinez-Hernandez. (1978). The basement membrane pores. In N. A. Kefalides (Ed.), *Biology and Chemistry of Basement Membranes* (pp. 99–109). Academic Press.

Behndig, A. (2008). Corneal endothelial integrity in aging mice lacking superoxide dismutase-1 and/or superoxide dismutase-3. *Molecular Vision*, *14*.

Behndig, A., Karlsson, K., Brännström, T., Sentman, M. L., & Marklund, S. L. (2001). Corneal endothelial integrity in mice lacking extracellular superoxide dismutase. *Investigative Ophthalmology and Visual Science*, *42*(12).

Belligoli, A., Compagnin, C., Sanna, M., Favaretto, F., Fabris, R., Busetto, L., Foletto, M., Dal Prà, C., Serra, R., Prevedello, L., da Re, C., Bardini, R., Mescoli, C., Rugge, M., Fioretto, P., Conci, S., Bettini, S., Milan, G., & Vettor, R. (2019). Characterization of subcutaneous and omental adipose tissue in patients with obesity and with different degrees of glucose impairment. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-47719-y

Carlson, E. C., Audette, J. L., Veitenheimer, N. J., Risan, J. A., Laturnus, D. I., & Epstein, P. N. (2003). Ultrastructural morphometry of capillary basement membrane thickness in normal and transgenic diabetic mice. *Anatomical Record - Part A Discoveries in Molecular, Cellular, and Evolutionary Biology*, *271*(2). https://doi.org/10.1002/ar.a.10038

Carpita, N., Sabularse, D., Montezinos, D., & Delmer, D. P. (1979). Determination of the pore size of cell walls of living plant cells. *Science*, *205*(4411). https://doi.org/10.1126/science.205.4411.1144

Ceafalan, L. C., Fertig, T. E., Gheorghe, T. C., Hinescu, M. E., Popescu, B. O., Pahnke, J., & Gherghiceanu, M. (2019). Age-related ultrastructural changes of the basement membrane in the mouse blood-brain barrier. *Journal of Cellular and Molecular Medicine*, *23*(2). https://doi.org/10.1111/jcmm.13980

Chen, M. J., & Mayo, K. H. (1991). Human Platelet Factor 4 Subunit Association/Dissociation Thermodynamics and Kinetics. *Biochemistry*, *30*(26). https://doi.org/10.1021/bi00240a009

Chen, R. R., Silva, E. A., Yuen, W. W., Brock, A. A., Fischbach, C., Lin, A. S., Guldberg, R. E., & Mooney, D. J. (2007). Integrated approach to designing growth factor delivery systems. *The FASEB Journal*, *21*(14). https://doi.org/10.1096/fj.06-7873com

Cinti, S. (2018). Obesity, Type 2 Diabetes and the Adipose Organ. In *Obesity, Type 2 Diabetes and the Adipose Organ*. https://doi.org/10.1007/978-3-319-40522-3

Comley, K., & Fleck, N. A. (2010). A micromechanical model for the Young’s modulus of adipose tissue. *International Journal of Solids and Structures*, *47*(21). https://doi.org/10.1016/j.ijsolstr.2010.07.001

Creutzfeldt, W., Mende, D., Willms, B., & Söling, H. D. (1970). Vascular basement membrane thickness in muscle of spiny mice and activities of glycolysis and gluconeogenesis in the liver of animals with spontaneous and experimental diabetes and of untreated human diabetics. *Diabetologia*, *6*(3). https://doi.org/10.1007/BF01212249

Cunningham, S. A., Tran, T. M., Arrate, M. P., & Brock, T. A. (1999). Characterization of vascular endothelial cell growth factor interactions with the kinase insert domain-containing receptor tyrosine kinase. A real time kinetic study. *Journal of Biological Chemistry*, *274*(26). https://doi.org/10.1074/jbc.274.26.18421

Cuthbertson, R. A., & Mandel, T. E. (1986). Anatomy of the mouse retina. Capillary basement membrane thickness. *Investigative Ophthalmology and Visual Science*, *27*(11).

Danis, R. P., & Yang, Y. (1993). Microvascular retinopathy in the Zucker diabetic fatty rat. *Investigative Ophthalmology and Visual Science*, *34*(7).

Darke, P. L., Jordan, S. P., Hall, D. L., Zugay, J. A., Shafer, J. A., & Kuo, L. C. (1994). Dissociation and Association of the HIV-1 Protease Dimer Subunits: Equilibria and Rates. *Biochemistry*, *33*(1). https://doi.org/10.1021/bi00167a013

Dembo, M., Kagey-Sobotka, A., Lichtenstein, L. M., & Goldstein, B. (1982). Kinetic analysis of histamine release due to covalently linked ige dimers. *Molecular Immunology*, *19*(3). https://doi.org/10.1016/0161-5890(82)90208-5

Digirolamo, M., & Owens, J. L. (1976). Water content of rat adipose tissue and isolated adipocytes in relation to cell size. *American Journal of Physiology*, *231*(5 (I)). https://doi.org/10.1152/ajplegacy.1976.231.5.1568

Dijkman, P. M., Castell, O. K., Goddard, A. D., Munoz-Garcia, J. C., de Graaf, C., Wallace, M. I., & Watts, A. (2018). Dynamic tuneable G protein-coupled receptor monomer-dimer populations. *Nature Communications*, *9*(1). https://doi.org/10.1038/s41467-018-03727-6

Eigenmann, M. J., Karlsen, T. v., Krippendorff, B. F., Tenstad, O., Fronton, L., Otteneder, M. B., & Wiig, H. (2017). Interstitial IgG antibody pharmacokinetics assessed by combined in vivo- and physiologically-based pharmacokinetic modelling approaches. *Journal of Physiology*, *595*(24). https://doi.org/10.1113/JP274819

Eppler, S. M., Combs, D. L., Henry, T. D., Lopez, J. J., Ellis, S. G., Yi, J. H., Annex, B. H., McCluskey, E. R., & Zioncheck, T. F. (2002). A target-mediated model to describe the pharmacokinetics and hemodynamic effects of recombinant human vascular endothelial growth factor in humans. *Clinical Pharmacology and Therapeutics*, *72*(1). https://doi.org/10.1067/mcp.2002.126179

Farquhar, M. G., & Palade, G. E. (1965). Cell junctions in amphibian skin. *The Journal of Cell Biology*, *26*(1). https://doi.org/10.1083/jcb.26.1.263

Filion, R. J., & Popel, A. S. (2004). A reaction-diffusion model of basic fibroblast growth factor interactions with cell surface receptors. *Annals of Biomedical Engineering*, *32*(5). https://doi.org/10.1023/B:ABME.0000030231.88326.78

Finley, S. D., Engel-Stefanini, M. O., Imoukhuede, P. I., & Popel, A. S. (2011). Pharmacokinetics and pharmacodynamics of VEGF-neutralizing antibodies. *BMC Systems Biology*, *5*. https://doi.org/10.1186/1752-0509-5-193

Fraselle-Jacobs, A., Jeanjean, M., Hauser, N., & Remacle, C. (1987). Effect of aging on the morphology of epididymal adipose tissue in the rat. *Experimental Gerontology*, *22*(6). https://doi.org/10.1016/0531-5565(87)90020-9

Fuh, G., Garcia, K. C., & de Vos, A. M. (2000). The interaction of neuropilin-1 in vascular endothelial growth factor and its receptor Flt-1. *Journal of Biological Chemistry*, *275*(35). https://doi.org/10.1074/jbc.M003955200

George, E. M., Liu, H., Robinson, G. G., Mahdi, F., Perkins, E., & Bidwell, G. L. (2015). Growth factor purification and delivery systems (PADS) for therapeutic angiogenesis. *Vascular Cell*, *7*(1). https://doi.org/10.1186/s13221-014-0026-3

Geretti, E., Shimizu, A., Kurschat, P., & Klagsbrun, M. (2007). Site-directed mutagenesis in the B-neuropilin-2 domain selectively enhances its affinity to VEGF165, but not to semaphorin 3F. *Journal of Biological Chemistry*, *282*(35). https://doi.org/10.1074/jbc.M702942200

Gluzman-Poltorak, Z., Cohen, T., Herzog, Y., & Neufeld, G. (2000). Neuropilin-2 and neuropilin-1 are receptors for the 165-amino acid form of vascular endothelial growth factor (VEGF) and of placenta growth factor-2, but only neuropilin-2 functions as a receptor for the 145-amino acid form of VEGF. *Journal of Biological Chemistry*, *275*(24). https://doi.org/10.1074/jbc.M909259199

Haas, T. L., & Duling, B. R. (1997). Morphology favors an endothelial cell pathway for longitudinal conduction within arterioles. *Microvascular Research*, *53*(2). https://doi.org/10.1006/mvre.1996.1999

Huang, X., Gottstein, C., Brekken, R. A., & Thorpe, P. E. (1998). Expression of soluble VEGF receptor 2 and characterization of its binding by surface plasmon resonance. *Biochemical and Biophysical Research Communications*, *252*(3). https://doi.org/10.1006/bbrc.1998.9717

Kleinheinz, J., Jung, S., Wermker, K., Fischer, C., & Joos, U. (2010). Release kinetics of VEGF165from a collagen matrix and structural matrix changes in a circulation model. *Head and Face Medicine*, *6*(1). https://doi.org/10.1186/1746-160X-6-17

Lash, J. M., Sherman, W. M., & Hamlin, R. L. (1989). Capillary basement membrane thickness and capillary density in sedentary and trained obese Zucker rats. *Diabetes*, *38*(7). https://doi.org/10.2337/diab.38.7.854

Lijnen, H. R., Christiaens, V., Scroyen, I., Voros, G., Tjwa, M., Carmeliet, P., & Collen, D. (2006). Impaired adipose tissue development in mice with inactivation of placental growth factor function. *Diabetes*, *55*(10). https://doi.org/10.2337/db06-0526

Lijnen, H. R., Demeulemeester, D., Van Hoef, B., Collen, D., & Maquoi, E. (2003). Deficiency of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) impairs nutritionally induced obesity in mice. *Thrombosis and Haemostasis*, *89*(2). https://doi.org/10.1055/s-0037-1613439

Lijnen, H. R., Frederix, L., & Scroyen, I. (2007). Deficiency of plasminogen activator inhibitor-2 impairs nutritionally induced murine adipose tissue development. *Journal of Thrombosis and Haemostasis*, *5*(11). https://doi.org/10.1111/j.1538-7836.2007.02735.x

Lijnen, H. R., Maquoi, E., Holvoet, P., Mertens, A., Lupu, F., Morange, P., Alessi, M. C., & Juhan-Vague, I. (2001). Adipose tissue expression of gelatinases in mouse models of obesity. *Thrombosis and Haemostasis*, *85*(6). https://doi.org/10.1055/s-0037-1615971

Lijnen, H. R., Maquoi, E., Morange, P., Voros, G., Van Hoef, B., Kopp, F., Collen, D., Juhan-Vague, I., & Alessi, M. C. (2003). Nutritionally induced obesity is attenuated in transgenic mice overexpressing plasminogen activator inhibitor-1. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *23*(1). https://doi.org/10.1161/01.ATV.0000044457.60665.DD

Lim, D. K., Wylie, R. G., Langer, R., & Kohane, D. S. (2016). Selective binding of C-6 OH sulfated hyaluronic acid to the angiogenic isoform of VEGF165. *Biomaterials*, *77*. https://doi.org/10.1016/j.biomaterials.2015.10.074

mac Gabhann, F., & Popel, A. S. (2004). Model of competitive binding of vascular endothelial growth factor and placental growth factor to VEGF receptors on endothelial cells. *American Journal of Physiology - Heart and Circulatory Physiology*, *286*(1 55-1). https://doi.org/10.1152/ajpheart.00254.2003

mac Gabhann, F., & Popel, A. S. (2005). Differential binding of VEGF isoforms to VEGF receptor 2 in the presence of neuropilin-1: A computational model. *American Journal of Physiology - Heart and Circulatory Physiology*, *288*(6 57-6). https://doi.org/10.1152/ajpheart.01218.2004

Mamer, S. B., Palasz, A. A., & Imoukhuede, P. I. (2019). Mapping tyrosine kinase receptor dimerization to receptor expression and ligand affinities. *Processes*, *7*(5). https://doi.org/10.3390/pr7050288

Mamer, S. B., Wittenkeller, A., & Imoukhuede, P. I. (2020). VEGF-A splice variants bind VEGFRs with differential affinities. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-71484-y

Maquoi, E., Demeulemeester, D., Vörös, G., Collen, D., & Lijnen, H. R. (2003). Enhanced nutritionally induced adipose tissue development in mice with stromelysin-I gene inactivation. *Thrombosis and Haemostasis*, *89*(4). https://doi.org/10.1055/s-0037-1613586

Maquoi, E., Munaut, C., Colige, A., Collen, D., & Roger Lijnen, H. (2002). Modulation of adipose tissue expression of murine matrix metalloproteinases and their tissue inhibitors with obesity. *Diabetes*, *51*(4). https://doi.org/10.2337/diabetes.51.4.1093

Marilyn G. Farquhar. (1978). Structure and function in glomerular capillaries: Role of the basement membrane in glomerular filtration. In N. A. Kefalides (Ed.), *Biology and Chemistry of Basement Membranes* (pp. 43–80). Academic Press.

Moore, J. M. R., Patapoff, T. W., & Cromwell, M. E. M. (1999). Kinetics and thermodynamics of dimer formation and dissociation for a recombinant humanized monoclonal antibody to vascular endothelial growth factor. *Biochemistry*, *38*(42). https://doi.org/10.1021/bi9905516

Morange, P. E., Lijnen, H. R., Alessi, M. C., Kopp, F., Collen, D., & Juhan-Vague, I. (2000). Influence of PAI-1 on adipose tissue growth and metabolic parameters in a murine model of diet-induced obesity. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *20*(4). https://doi.org/10.1161/01.ATV.20.4.1150

Mota, F., Yelland, T., Hutton, J. A., Parker, J., Patsiarika, A., Chan, A. W. E., O’Leary, A., Fotinou, C., Martin, J. F., Zachary, I. C., Djordjevic, S., Frankel, P., & Selwood, D. L. (2022). Peptides Derived from Vascular Endothelial Growth Factor B Show Potent Binding to Neuropilin-1. *ChemBioChem*, *23*(1). https://doi.org/10.1002/cbic.202100463

Nugent, M. A., & Edelmant, E. R. (1992). Kinetics of Basic Fibroblast Growth Factor Binding to Its Receptor and Heparan Sulfate Proteoglycan: A Mechanism for Cooperativity. *Biochemistry*, *31*(37). https://doi.org/10.1021/bi00152a026

Olofsson, B., Korpelainen, E., Pepper, M. S., Mandriota, S. J., Aase, K., Kumar, V., Gunji, Y., Jeltsch, M. M., Shibuya, M., Alitalo, K., & Eriksson, U. (1998). Vascular endothelial growth factor B (VEGF-B) binds to VEGF receptor-1 and regulates plasminogen activator activity in endothelial cells. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(20). https://doi.org/10.1073/pnas.95.20.11709

Pan, Q., Chathery, Y., Wu, Y., Rathore, N., Tong, R. K., Peale, F., Bagri, A., Tessier-Lavigne, M., Koch, A. W., & Watts, R. J. (2007). Neuropilin-1 binds to VEGF121 and regulates endothelial cell migration and sprouting. *Journal of Biological Chemistry*, *282*(33). https://doi.org/10.1074/jbc.M703554200

Papo, N., Silverman, A. P., Lahti, J. L., & Cochran, J. R. (2011). Antagonistic VEGF variants engineered to simultaneously bind to and inhibit VEGFR2 and α vβ 3 integrin. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(34). https://doi.org/10.1073/pnas.1016635108

Patapoff, T. W., Mrsny, R. J., & Lee, W. A. (1993). The Application of size exclusion chromatography and computer simulation to study the thermodynamic and kinetic parameters for short-lived dissociable protein aggregates. *Analytical Biochemistry*, *212*(1). https://doi.org/10.1006/abio.1993.1293

Rodrigues, M., Currier, C., & Yoon, J. (1983). Electron microscopy of renal and ocular changes in virus-induced diabetes mellitus in mice. *Diabetologia*, *24*(4). https://doi.org/10.1007/BF00282717

Sarin, H. (2010). Physiologic upper limits of pore size of different blood capillary types and another perspective on the dual pore theory of microvascular permeability. *Journal of Angiogenesis Research*, *2*(1). https://doi.org/10.1186/2040-2384-2-14

Serini, G., Ambrosi, D., Giraudo, E., Gamba, A., Preziosi, L., & Bussolino, F. (2003). Modeling the early stages of vascular network assembly. *EMBO Journal*, *22*(8). https://doi.org/10.1093/emboj/cdg176

Simionescu, N., Simionescu, M., & Palade, G. E. (1978). Structural basis of permeability in sequential segments of the microvasculature of the diaphragm. II. Pathways followed by microperoxidase across the endothelium. *Microvascular Research*, *15*(1). https://doi.org/10.1016/0026-2862(78)90002-X

Soker, S., Fidder, H., Neufeld, G., & Klagsbrun, M. (1996). Characterization of novel vascular endothelial growth factor (VEGF) receptors on tumor cells that bind VEGF165 via its exon 7-encoded domain. *Journal of Biological Chemistry*, *271*(10). https://doi.org/10.1074/jbc.271.10.5761

Soker, S., Takashima, S., Miao, H. Q., Neufeld, G., & Klagsbrun, M. (1998). Neuropilin-1 is expressed by endothelial and tumor cells as an isoform- specific receptor for vascular endothelial growth factor. *Cell*, *92*(6). https://doi.org/10.1016/S0092-8674(00)81402-6

Song, M., Liu, Y., & Hui, L. (2018). Preparation and characterization of acellular adipose tissue matrix using a combination of physical and chemical treatments. *Molecular Medicine Reports*, *17*(1). https://doi.org/10.3892/mmr.2017.7857

Tan, W. H., Popel, A. S., & mac Gabhann, F. (2013a). Computational Model of Gab1/2-Dependent VEGFR2 Pathway to Akt Activation. *PLoS ONE*, *8*(6). https://doi.org/10.1371/journal.pone.0067438

Tan, W. H., Popel, A. S., & mac Gabhann, F. (2013b). Computational model of VEGFR2 pathway to ERK activation and modulation through receptor trafficking. *Cellular Signalling*, *25*(12). https://doi.org/10.1016/j.cellsig.2013.08.015

Teran, M., & Nugent, M. A. (2019). Characterization of receptor binding kinetics for vascular endothelial growth factor-A using SPR. *Analytical Biochemistry*, *564–565*. https://doi.org/10.1016/j.ab.2018.10.001

van den Berg, B. M., Vink, H., & Spaan, J. A. E. (2003). The endothelial glycocalyx protects against myocardial edema. *Circulation Research*, *92*(6). https://doi.org/10.1161/01.RES.0000065917.53950.75

Van Hul, M., Frederix, L., & Roger Lijnen, H. (2012). Role of thrombospondin-2 in murine adipose tissue angiogenesis and development. *Obesity*, *20*(9). https://doi.org/10.1038/oby.2011.260

von Tiedemann, B., & Bilitewski, U. (2002). Characterization of the vascular endothelial growth factor-receptor interaction and determination of the recombinant protein by an optical receptor sensor. *Biosensors and Bioelectronics*, *17*(11–12). https://doi.org/10.1016/S0956-5663(02)00090-8

Voros, G., Maquoi, E., Demeulemeester, D., Clerx, N., Collen, D., & Lijnen, H. R. (2005). Modulation of angiogenesis during adipose tissue development in murine models of obesity. *Endocrinology*, *146*(10). https://doi.org/10.1210/en.2005-0532

Waltenberger, J., Claesson-Welsh, L., Siegbahn, A., Shibuya, M., & Heldin, C. H. (1994). Different signal transduction properties of KDR and Flt1, two receptors for vascular endothelial growth factor. *Journal of Biological Chemistry*, *269*(43). https://doi.org/10.1016/s0021-9258(18)47116-5

Weddell, J. C., & Imoukhuede, P. I. (2017). Integrative meta-modeling identifies endocytic vesicles, late endosome and the nucleus as the cellular compartments primarily directing RTK signaling. *Integrative Biology (United Kingdom)*, *9*(5). https://doi.org/10.1039/c7ib00011a

Whitaker, G. B., Limberg, B. J., & Rosenbaum, J. S. (2001). Vascular Endothelial Growth Factor Receptor-2 and Neuropilin-1 Form a Receptor Complex that is Responsible for the Differential Signaling Potency of VEGF165 and VEGF121. *Journal of Biological Chemistry*, *276*(27). https://doi.org/10.1074/jbc.M102315200

Yen, P., Finley, S. D., Engel-Stefanini, M. O., & Popel, A. S. (2011). A two-compartment model of VEGF distribution in the mouse. *PLoS ONE*, *6*(11). https://doi.org/10.1371/journal.pone.0027514