|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 |
| Macrophage | Diameter of one cell | Search | O |
| Surface area of one cell | Calculate | - |
| Volume of one cell | Calculate | - |
| Total surface areas of macrophages | Calculate | - |
| The number of macrophages | Search |  |
| 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 |  |

* **Macrophage size**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Animal** | **Strain** | **Sex** | **n** | **Age** | **Diet** | **Body weight** | **Location** | **Method** | **Diameter** | **Volume** |
| (Krombach et al., 1997) | Rat | Sprague Dawley | Male | 12 | ? | SFD *ad libitum* | 250-350 g | Lung | 1. Harvest alveolar macrophage using bronchoalveolar lavage. 2. Measure the cell size using flow cytometric analysis. | 13.1±0.2 µm | 1166.0±41.5 µm3 |
| Hamster | Syrian golden | Male | 8 | ? | SFD *ad libitum* | 120-150 g | 13.6±0.4 µm | 1327.8±123.4 µm3 |
| Monkey | Adult cynomolgus | Both | 7 | ? | *ad libitum* | 3.5-7.0 kg | 15.5±0.5 µm | 1926.4±193.1 µm3 |
| Human | Non-smoking | Male | 10 | 25.6±1.2 y. | - | ? | 21.2±0.3 µm | 4989.9±174.0 µm3 |
| (Haley et al., 1991) | Mouse | B6C3F1 | Male | 4 | 10 wk. | *ad libitum* | ? | Lung | 1. Lavage alveolar macrophage using fiberoptic bronchoscope. 2. Centrifuge in a Shandon, Cytospin 2 cytocentrifuge 3. Use image analysis to measure the cell size. | 19±0.08 µm | ? |
| Rat | F344/Cr1 | Male | 4 | 10 wk. | *ad libitum* | ? | 18±0.08 µm | ? |
| Dog | Beagle | Male | 4 | 2 y. | *ad libitum* | ? | 16±0.09 µm | ? |
| Monkey | Cynomolgus | Male | 4 | ? | *ad libitum* | ? | 23±0.11 µm | ? |
| Chimpanzee | - | Male | 4 | 10 y. | *ad libitum* | ? | 23±0.11 µm | ? |
| Human | Non-smoking | Male | 4 | 24-34 y. | - | ? | 26±0.14 µm | ? |

* **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±37 |
| 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) | 61.87±1.33 nm |
| 6 | Genetic obesity (fa/fa) | 68.13±1.66 nm |
| 18 wk. | 6 | Lean (Fa/fa) | 55.67±1.04 nm |
| 7 | Genetic obesity (fa/fa) | 57.82±1.24 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 | 6 | Lean | ? | Visceral adipose tissue | Transmission electron microscopy (TEM) | 103.38 nm  [67.23, 194.26] |
| 41±9 y | 5 | Obese without diabetes | 108.78 nm  [60.47, 181.76] |
| 52±9 y | 5 | 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 |
| (Papadopoulos et al., 2012) | VEGF165 | Human  VEGFR1-hFc§ | SPR | | | **VEGF165**  Obtained from R&D systems  **Human VEGFR1-hFc**  Made at Regeneron Pharmaceuticals |  |  | pM |
| (Jin et al., 2007) | 125I-VEGF165 | VEGFR1 on adventitial fibroblasts | Radioligand  (Saturation analysis) | | | **VEGF165**  Obtained from PerkinElmer  **VEGFR1**  adventitial fibroblasts from thoracic aorta of 6–8-week-old male Sprague–Dawley (SD) rats | ? | ? | pM |
| (Breier et al., 1995) | Recombinant 125I-VEGF165 | VEGFR1 on COS cells | Radioligand  (Saturation  analysis) | Non-linear regression curve | | **VEGF165**  Expressed in Sf9 insect cells  **VEGFR1**  COS cells transfected with murine full length VEGFR1 cDNA | ? | ? | 90 pM |
| Scatchard analysis | | 114 pM |
| (Ito & Claesson-Welsh, 1999) | VEGF165 | VEGFR1 on PAE cells | Radioligand  (Saturation analysis) | | No heparin | **VEGF165**  From PeproTech. Inc  **VEGFR1**  PAE cells transfected with human VEGFR1 cDNA | ? | ? | 91.54 pM |
| Heparin 0.5 µg/ml | 159.64 pM |
| Heparin  5 µg/ml | 215.32 pM |
| (Rouet et al., 2005) | Recombinant 125I-VEGF165 | VEGFR1-Fc chimera† | ELISA plate+Saturation analysis | | | **VEGF165**  expressed in Sf9 insect cells  **VEGFR1**  R&D Systems | ? | ? | 59.4±19.6 pM |

\* Fc: pre-dimerized

§ The extracellular domains of dimerized human VEGFR1 or VEGFR2 fused inline to hFc

† The extracellular domain of VEGFR1

* **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 | ? | ? | 339120 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 |
| (Rouet et al., 2005) | Recombinant 125I-VEGF165 | VEGFR2-Fc chimera† | ELISA plate+Saturation analysis | **VEGF165**  expressed in Sf9 insect cells  **VEGFR2**  R&D Systems | ? | ? | 292.5±163.8  pM |
| (Terman et al., 1992) | Recombinant 125I-VEGF165 | VEGFR2 on CMT-3 cells | Radioligand  (Saturation analysis) | **VEGF165**  Cells transfected with an expression vector containing the VEGF cDNA encoding the 165 amino acid form of VEGF  **VEGFR2**  CMT-3 monkey kidney cells transfected with KDR gene | ? | ? | 75 pM |

\* Fc: pre-dimerized fusion protein

§ cbu: monomeric fusion protein

† The extracellular domain of VEGFR2

* **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 |
| (Gu et al., 2002) | Recombinant 125I-VEGF165 | NRP1 on COS-1 cells | Radioligand  (Saturation analysis) | **NRP1**  COS-1 cells transiently expressing the Npn-1 | ? | ? | 0.93±0.71 nM |
| (Rouet et al., 2005) | Recombinant 125I-VEGF165 | NRP1-Fc chimera† | ELISA plate+Saturation analysis | **VEGF165**  expressed in Sf9 insect cells  **NRP1**  R&D Systems | ? | ? | 246.4±135.1  pM |
| (Vintonenko et al., 2011) | Recombinant VEGF165 | Recombinant NRP1 | SPR | **NRP1**  R&D Systems |  |  |  |

\* 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.

† The extracellular domain of NRP1

* **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**

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