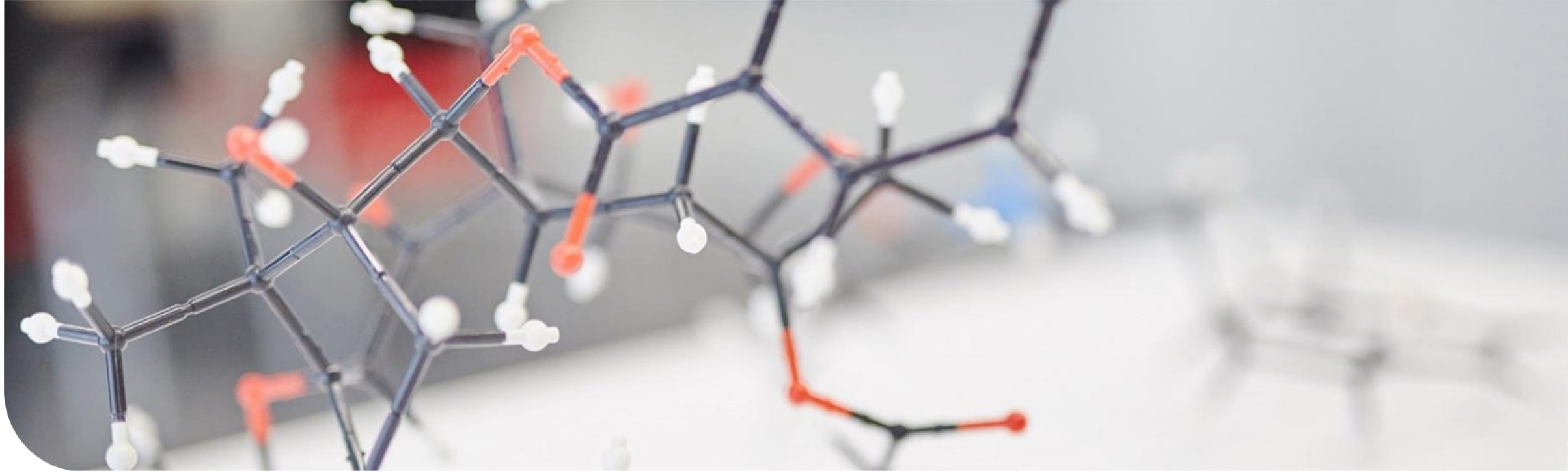
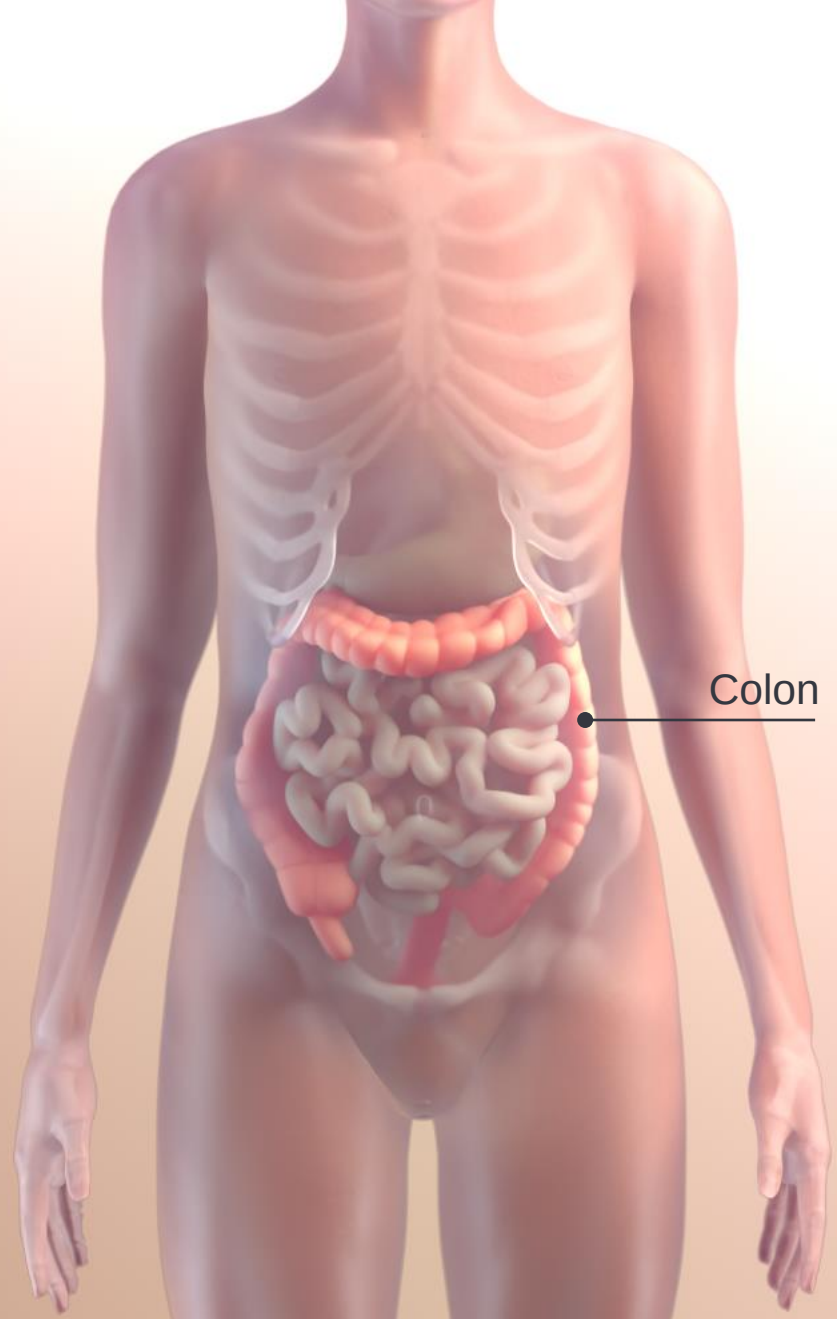


Fruquintinib Mechanism of Action

January 2024

VV-MEDMAT-99771

ONCOLOGY



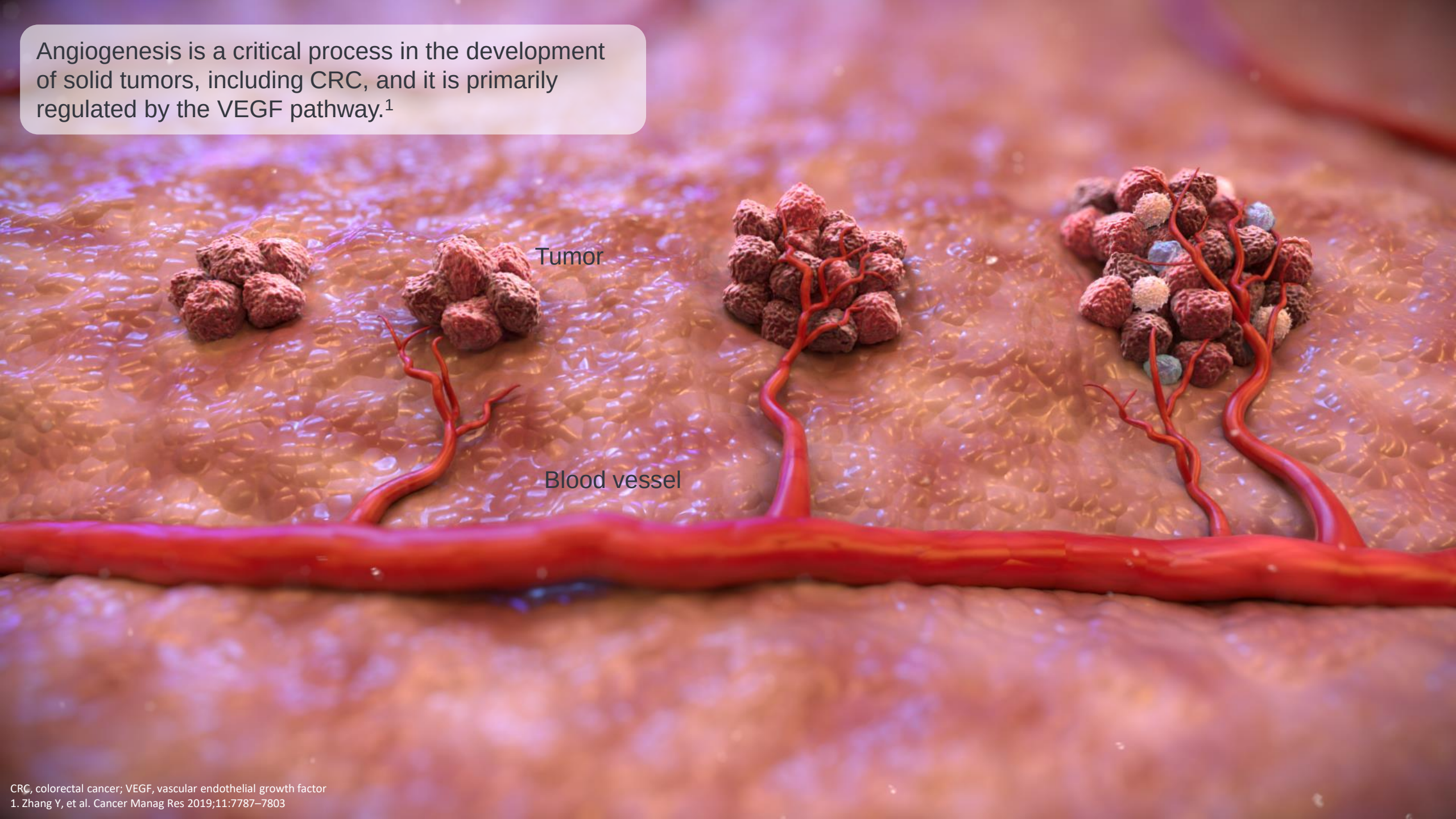
Fruquintinib is a kinase inhibitor of all three VEGF receptors and is approved in the US for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type and medically appropriate, an anti-EGFR therapy.[1,2]

Fruquintinib is approved for the treatment of previously treated metastatic colorectal cancer in the United States and China. In regions where it is not currently approved, there is no guarantee that it will receive regulatory approval

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor

1. Sun Q, et al. Cancer Biol Ther 2014;15:1635–45; 2. Fruzaqla (fruquintinib) US Prescribing Information. Takeda Pharmaceuticals America Inc. Nov 2023

Angiogenesis is a critical process in the development of solid tumors, including CRC, and it is primarily regulated by the VEGF pathway.[1]



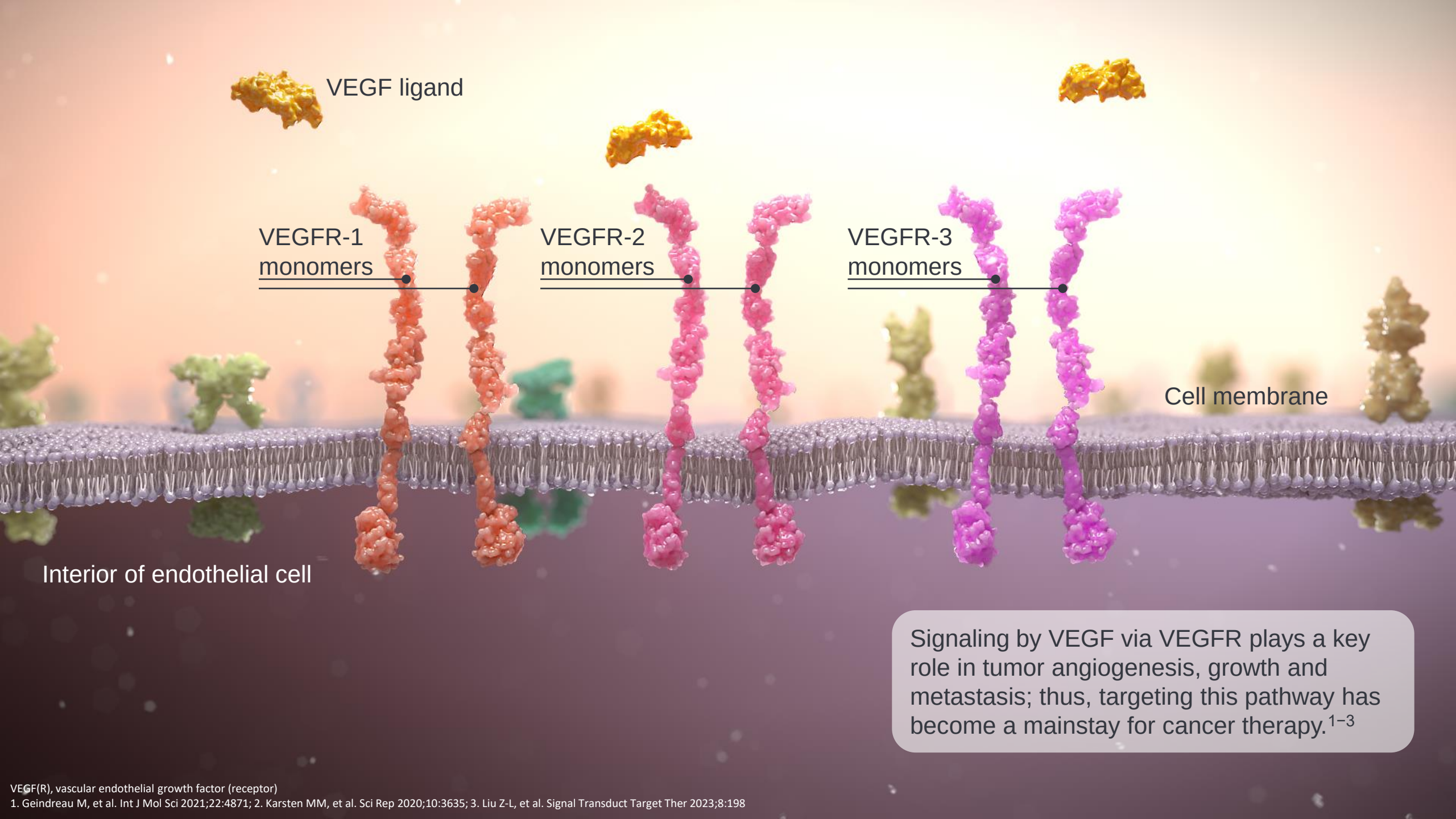
CRC, colorectal cancer; VEGF, vascular endothelial growth factor

1. Zhang Y, et al. Cancer Manag Res 2019;11:7787–7803

Release of VEGF by cancer cells results in an imbalance of proangiogenic factors in the tumor microenvironment, which activates the angiogenic switch and the formation of new blood vessels that allow oxygen and nutrients to reach the tumor, leading to tumor growth.[1,2]

VEGF, vascular endothelial growth factor

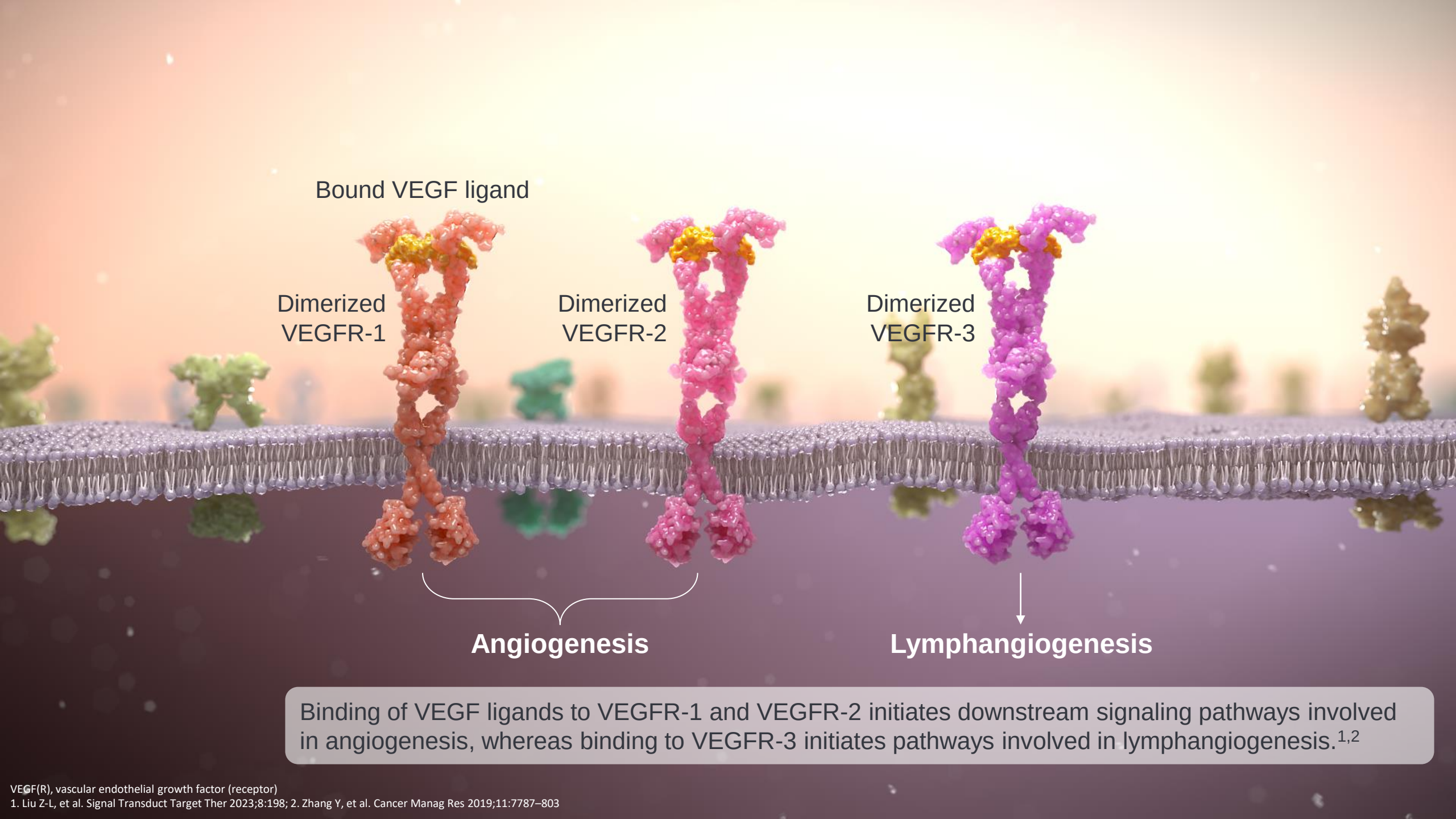
1. Geindreau M, et al. Int J Mol Sci 2021;22:4871; 2. Lee SH, et al. Ann Surg Treat Res 2015;89:1–8



Signaling by VEGF via VEGFR plays a key role in tumor angiogenesis, growth and metastasis; thus, targeting this pathway has become a mainstay for cancer therapy.[1–3]

VEGF(R), vascular endothelial growth factor (receptor)

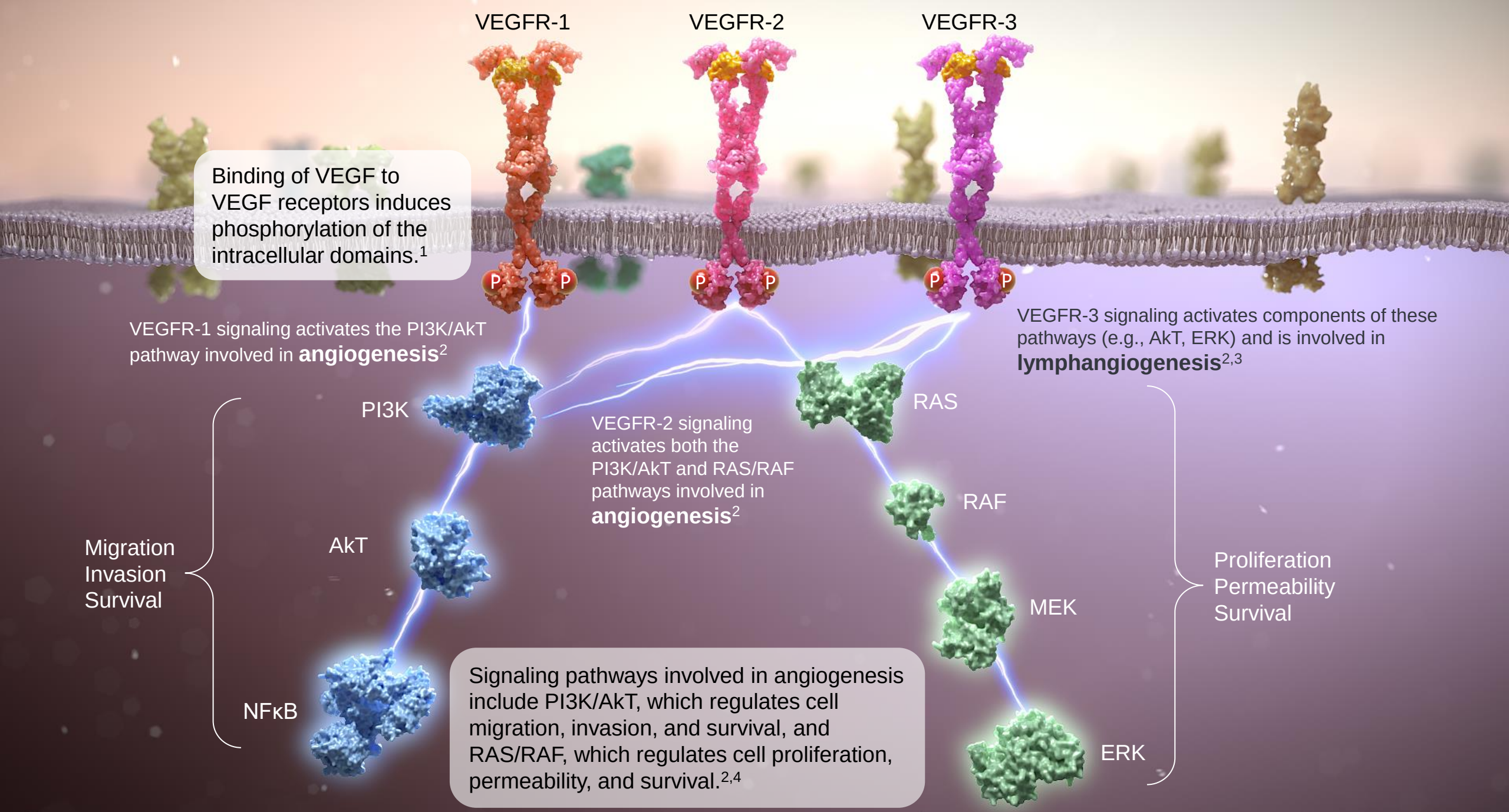
1. Geindreau M, et al. Int J Mol Sci 2021;22:4871; 2. Karsten MM, et al. Sci Rep 2020;10:3635; 3. Liu Z-L, et al. Signal Transduct Target Ther 2023;8:198



Binding of VEGF ligands to VEGFR-1 and VEGFR-2 initiates downstream signaling pathways involved in angiogenesis, whereas binding to VEGFR-3 initiates pathways involved in lymphangiogenesis.[1,2]

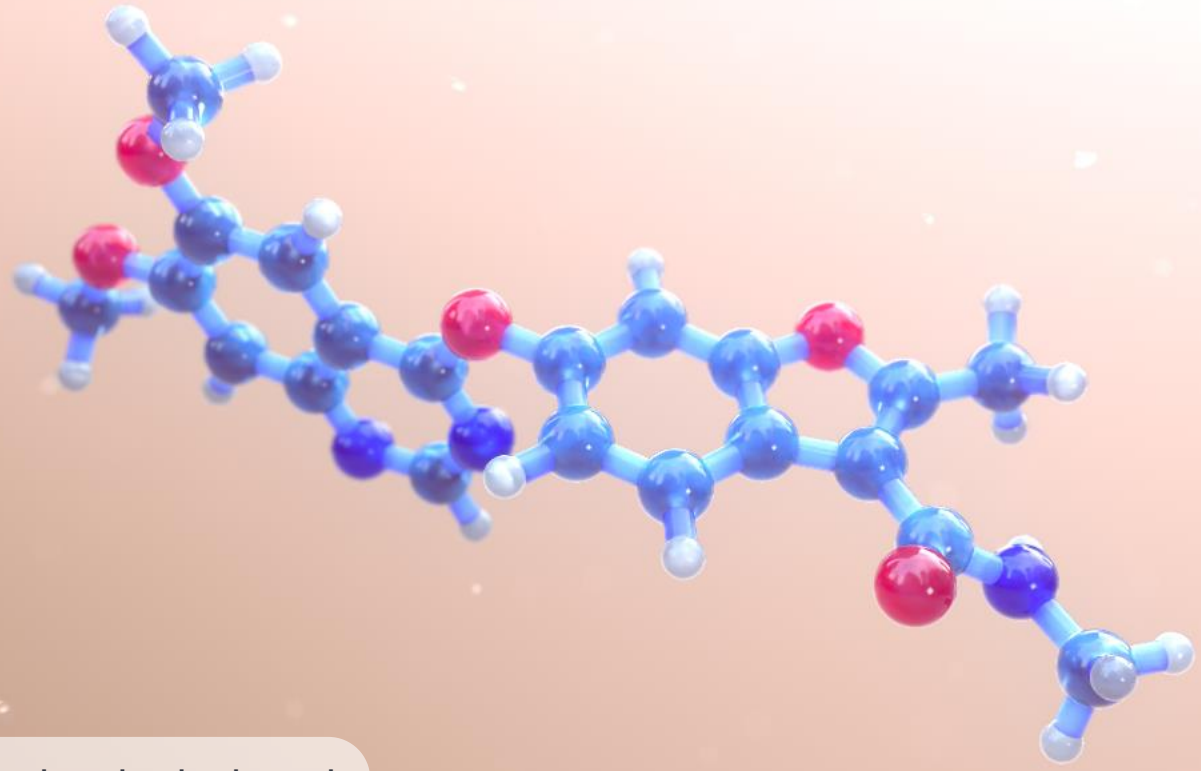
VEGF(R), vascular endothelial growth factor (receptor)

1. Liu Z-L, et al. Signal Transduct Target Ther 2023;8:198; 2. Zhang Y, et al. Cancer Manag Res 2019;11:7787–803



VEGF(R), vascular endothelial growth factor (receptor)

1. Park SA, et al. BMB Rep 2018;51:73–8; 2. Lopez A, et al. Drugs 2019;79:63–74; 3. Deng Y, et al. Arterioscler Thromb Vasc Biol 2015;35: 421–9; 4. Qin S, et al. J Hematol Oncol 2019;12:27

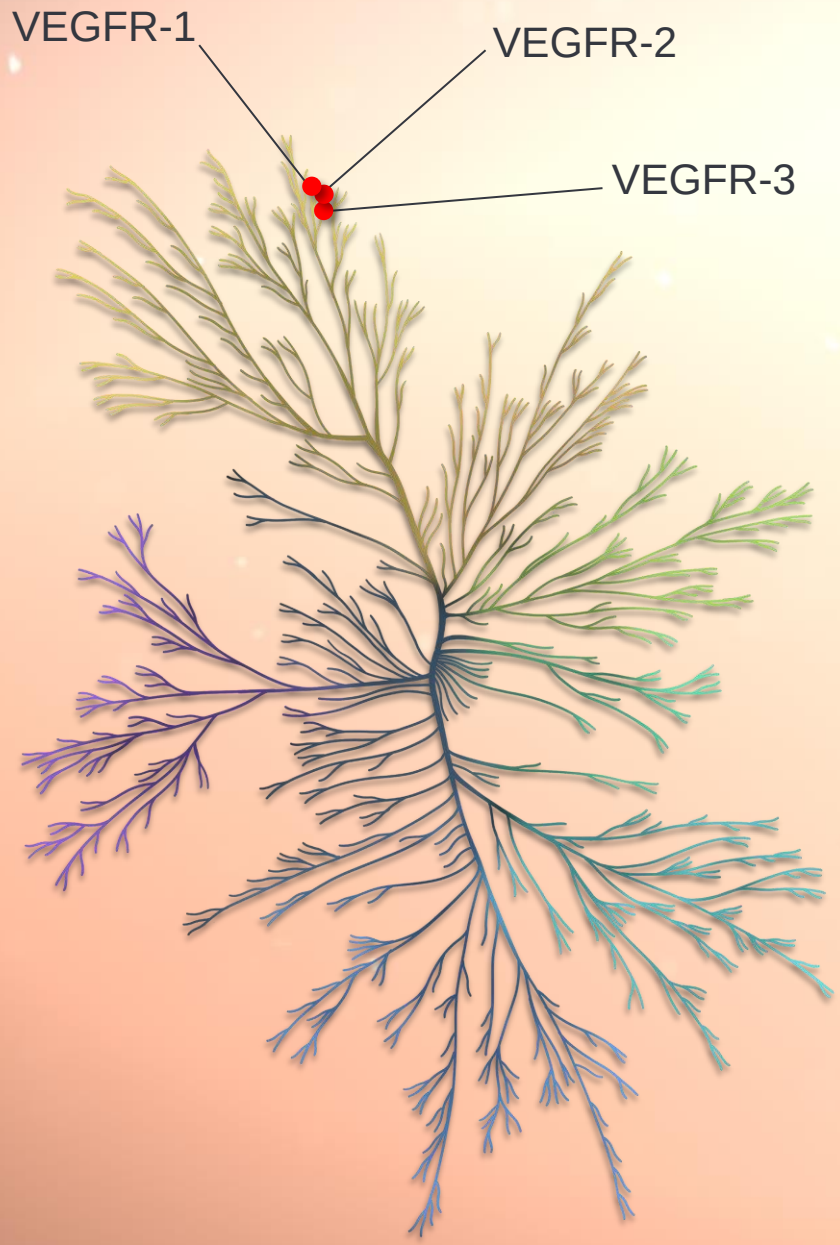


Fruquintinib is an oral small molecule designed to target only the three VEGF receptors (VEGFR-1, VEGFR-2, and VEGFR-3), blocking the VEGF pathway.[1]

Preclinical data may not indicate clinical efficacy. Clinical efficacy can only be confirmed through clinical trials

VEGF(R), vascular endothelial growth factor (receptor)

1. Sun Q, et al. Cancer Biol Ther 2014;15:1635–45

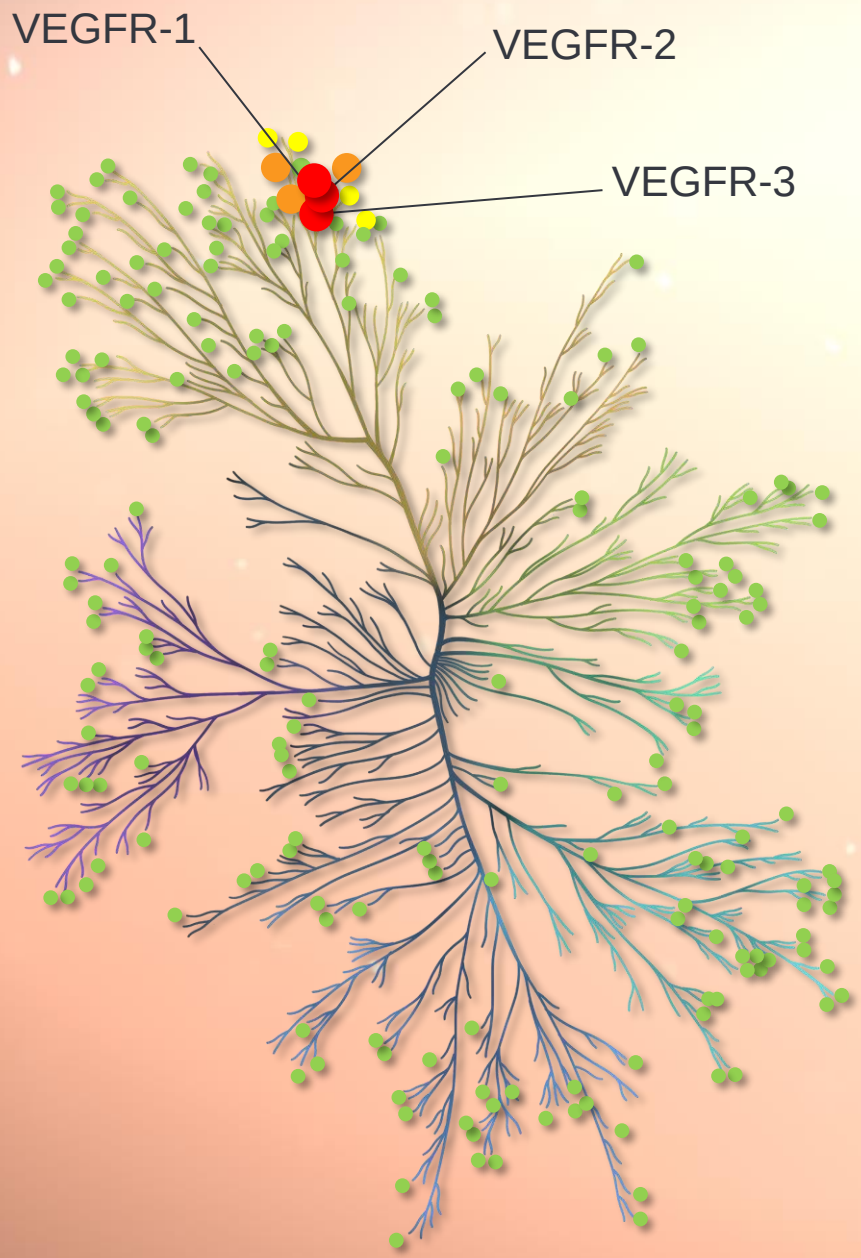


Unlike earlier-generation VEGFR inhibitors,* fruquintinib selectively inhibits the intracellular kinase domain of VEGFR-1, -2, and -3 at low nanomolar levels, while having weak to no inhibitory effect on all other kinases.[1]

Preclinical data may not indicate clinical efficacy. Clinical efficacy can only be confirmed through clinical trials

*Head-to-head trials have not been performed. VEGFR, vascular endothelial growth factor receptor

1. Sun Q, et al. Cancer Biol Ther 2014;15:1635–45



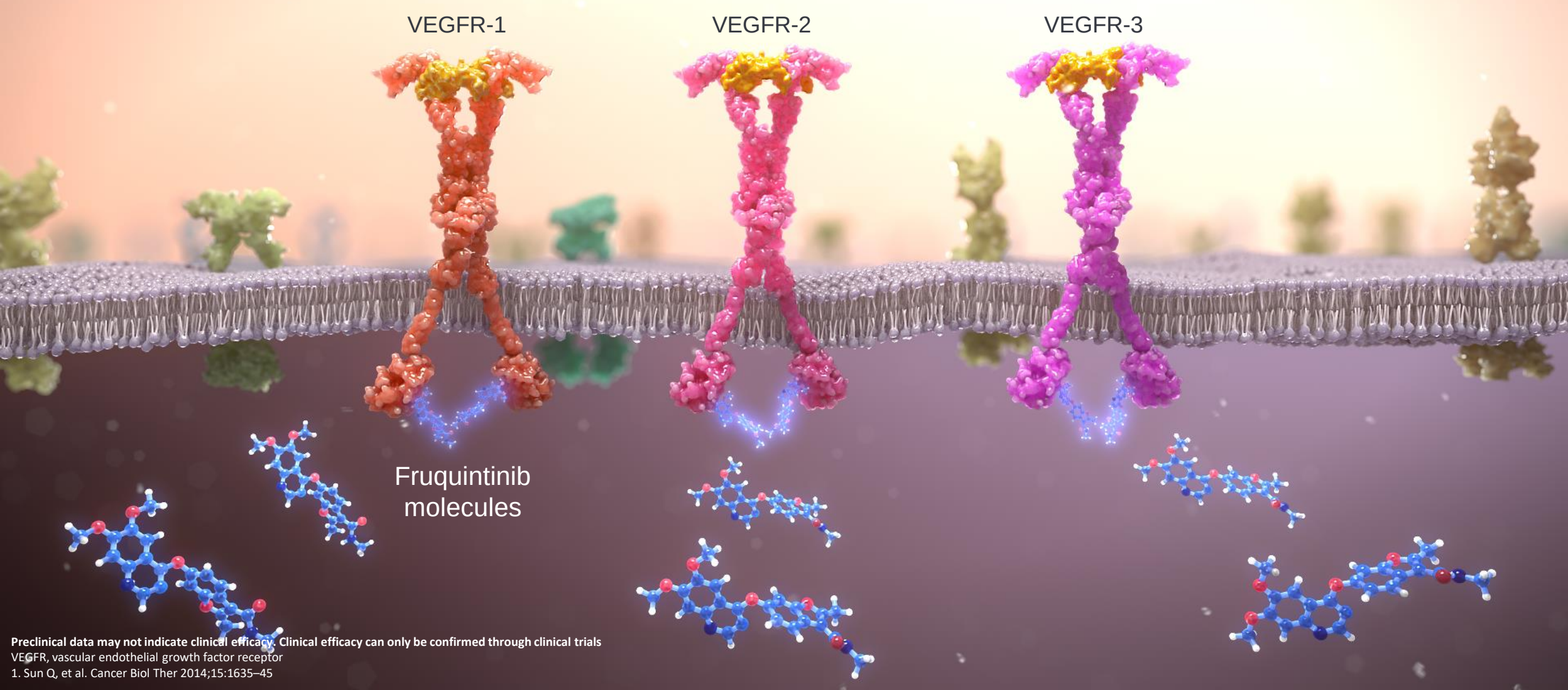
Unlike earlier-generation VEGFR inhibitors,† fruquintinib selectively inhibits the intracellular kinase domain of VEGFR-1, -2, and -3 at low nanomolar levels, while having weak to no inhibitory effect on all other kinases.[1]

Preclinical data may not indicate clinical efficacy. Clinical efficacy can only be confirmed through clinical trials

*Kinome selectivity of fruquintinib against a panel of 253 kinases; †Head-to-head trials have not been performed. VEGFR, vascular endothelial growth factor receptor

1. Sun Q, et al. Cancer Biol Ther 2014;15:1635–45

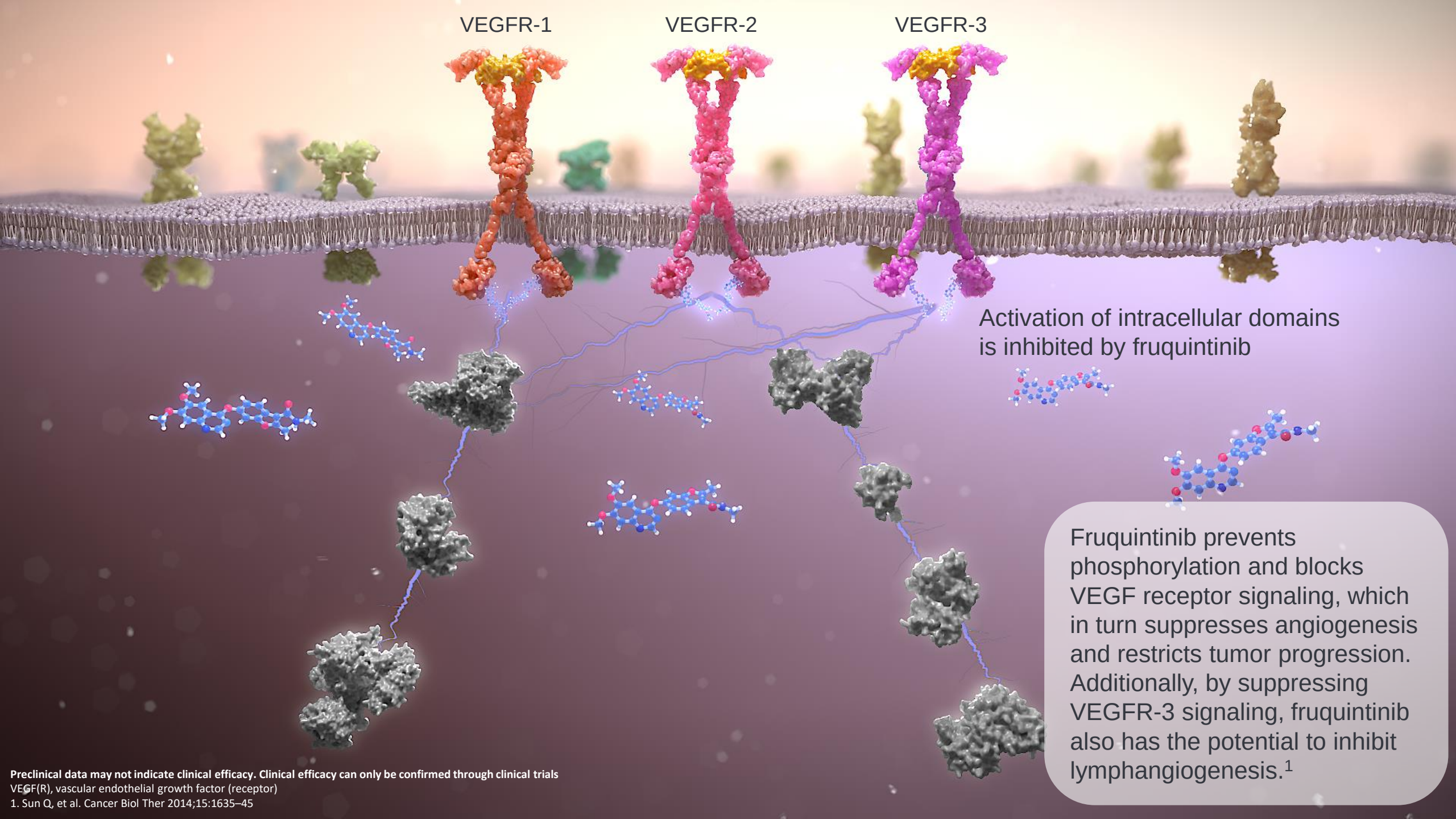
The enhanced selectivity of fruquintinib limits off-target kinase activity, allowing for high drug exposure and sustained target inhibition.[1]



Preclinical data may not indicate clinical efficacy. Clinical efficacy can only be confirmed through clinical trials

VEGFR, vascular endothelial growth factor receptor

1. Sun Q, et al. Cancer Biol Ther 2014;15:1635–45



Preclinical data may not indicate clinical efficacy. Clinical efficacy can only be confirmed through clinical trials

VEGF(R), vascular endothelial growth factor (receptor)

1. Sun Q, et al. Cancer Biol Ther 2014;15:1635–45