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ANTI-SYNDECAN-2 HUMAN MONOCLONAL ANTIBODY FOR TREATMENT OF STROKE-ASSOCIATED EDEMA

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American Stroke Association.
A division of the American Heart Association.

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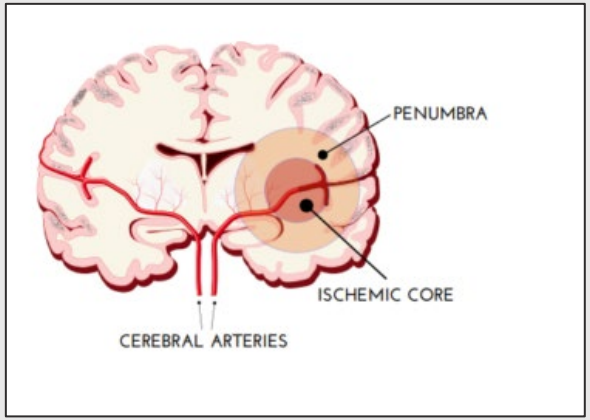
Federico Corti, PhD and Michael Simons, MD

Cofounders of VST Bio Ltd.

CONSEQUENCES OF BBB DISRUPTION IN ISCHEMIC STROKE



Loss of BBB integrity

VEGFA
(Vascular Endothelial Growth Factor A)

Brain swelling (edema)

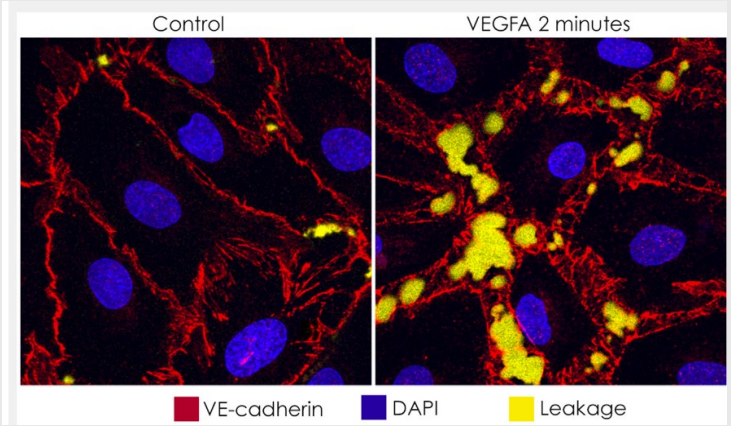
- Due to imbalanced water entry from blood circulation into the brain
- Increased brain compression and tissue damage
- Develops in few hours and it can be sustained from days to weeks

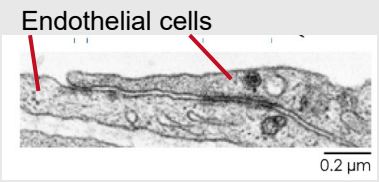
Neurotoxicity

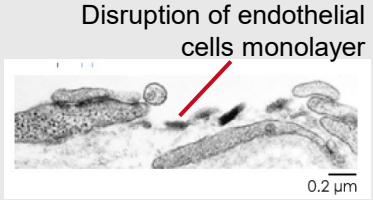
- Due to entry of pro-inflammatory/toxic proteins from blood into the brain
- Accelerated loss of the penumbra area and activation of local inflammation
- Increased ROS production and glutamate excitotoxicity

VEGFA IS A MAJOR DRIVER OF BBB DISRUPTION

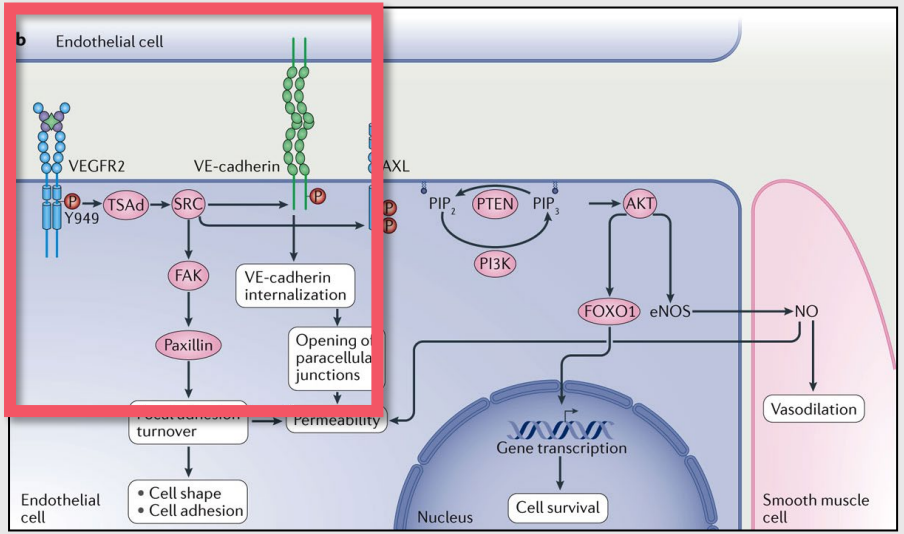
VEGFA levels strongly increases in ischemic stroke and promotes BBB disruption (leading to increased vascular permeability in the brain)







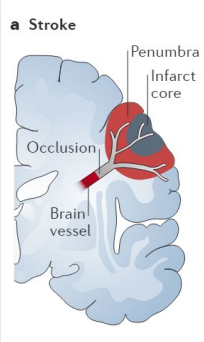
Claesson-Welsh at al. (2020) Permeability of the Endothelial Barrier: Identifying and Reconciling Controversies PMID:33309601

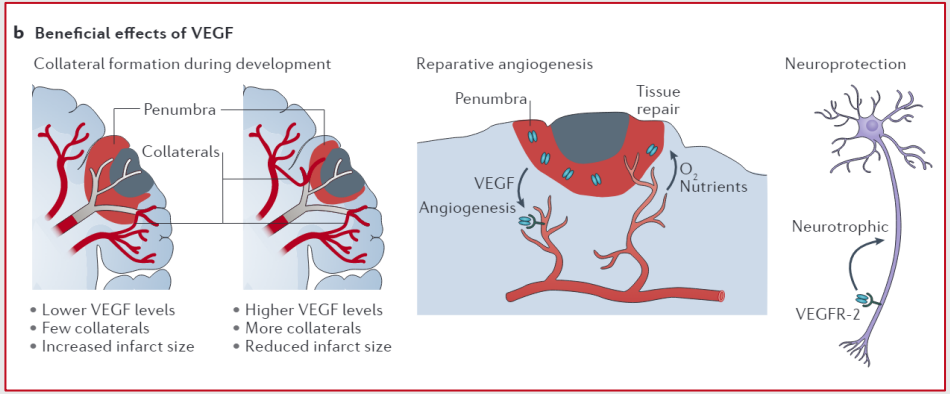


Simons et al. (2016) Mechanisms and regulation of endothelial VEGF receptor signalling. PMID: 27461391

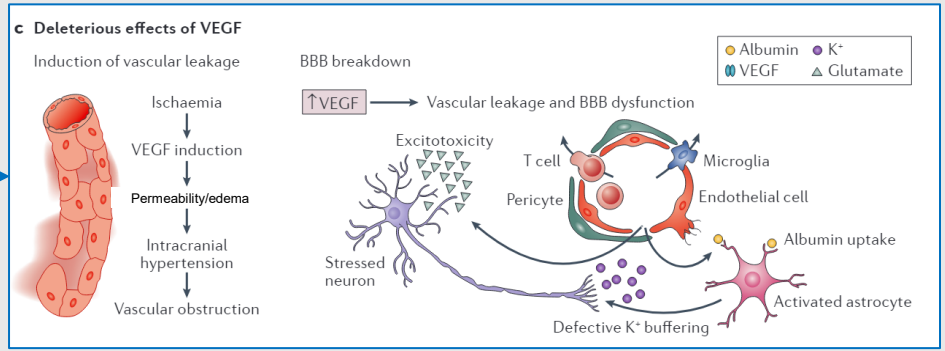
INHIBITION OF VEGFA ACTIVITY IN ISCHEMIC STROKE

It has been extensively investigated in animal models but requires a selective action against vascular permeability





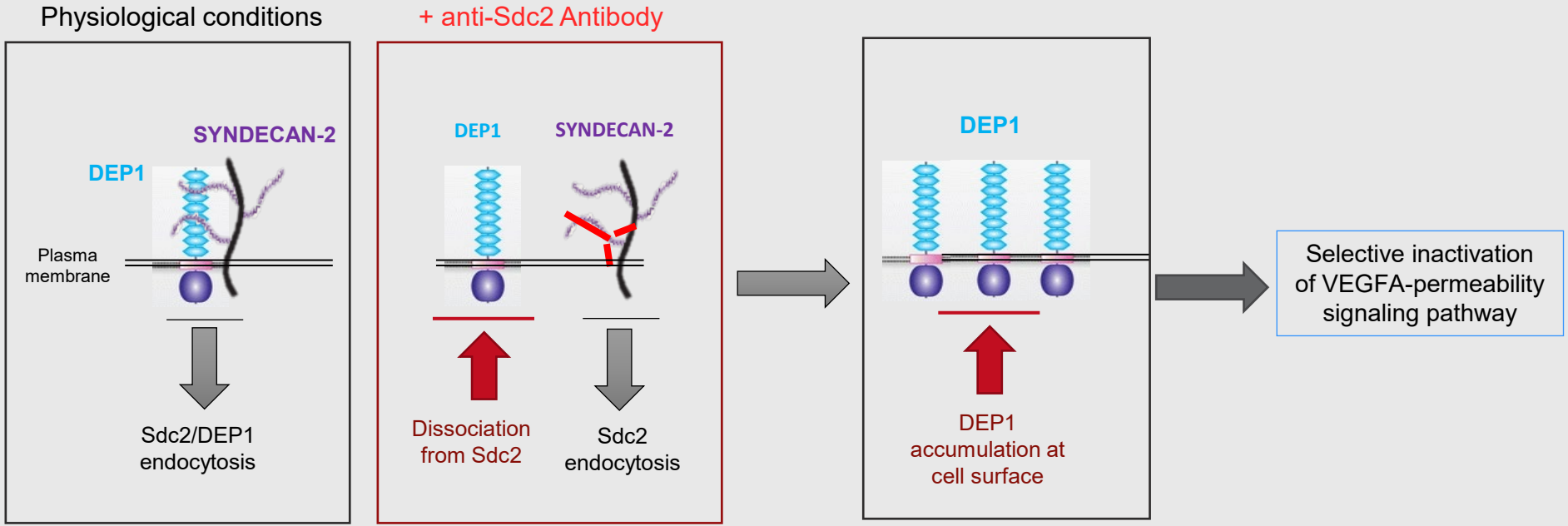
- ✓ Loss of neuroprotection and new blood vessel formation (angiogenesis)
- ✓ Loss of anti-apoptosis/pro-survival effects
- ✓ Reduction in endothelial viability



- ✓ Reduces brain swelling
- ✓ Improve salvage of penumbra area
- ✓ Reduce ROS accumulation in brain parenchyma
- ✓ Reduce risk of hemorrhagic transformation
- ✓ Reduces local and systemic inflammation

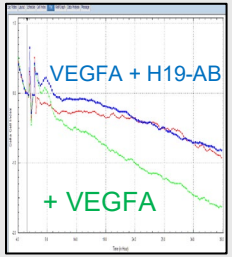
Lange et al. (2016) Vascular endothelial growth factor: a neurovascular target in neurological diseases. PMID: 27364743

A MECHANISM TO SELECTIVELY BLOCK VEGFA-INDUCED BBB DISRUPTION AND PERMEABILITY

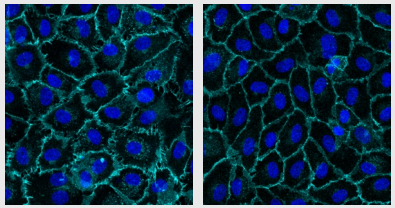


Corti et al. (2022) Syndecan-2 selectively regulates VEGF-induced vascular permeability. PMID: 36212522

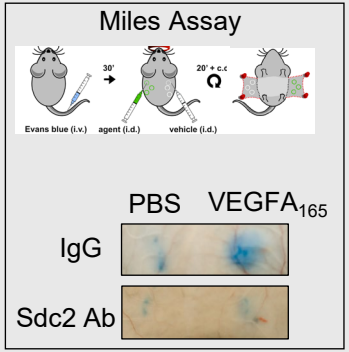
DEVELOPMENT OF AN ANTI-HUMAN SDC2 ANTIBODY THAT BLOCKS VEGFA-INDUCED BBB DISRUPTION

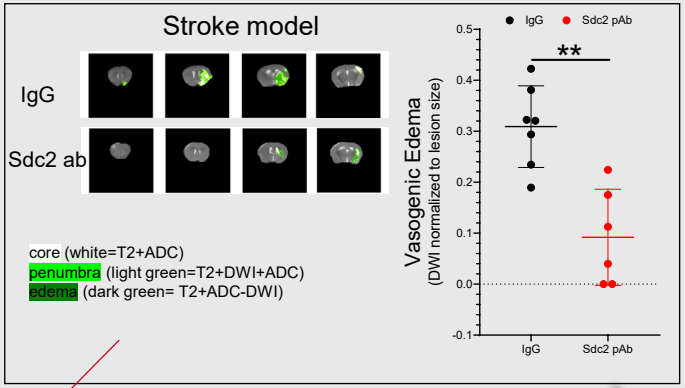


Screening by in vitro permeability assay (TEER analysis)



Additional in vitro characterization





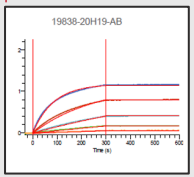
Early development

Mouse studies

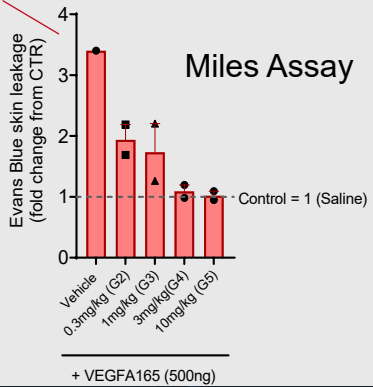
Non-Human Primate studies

Hybridoma campaign against human Sdc2 (and mouse Sdc2)

Kinetic analysis (nanomolar affinity)



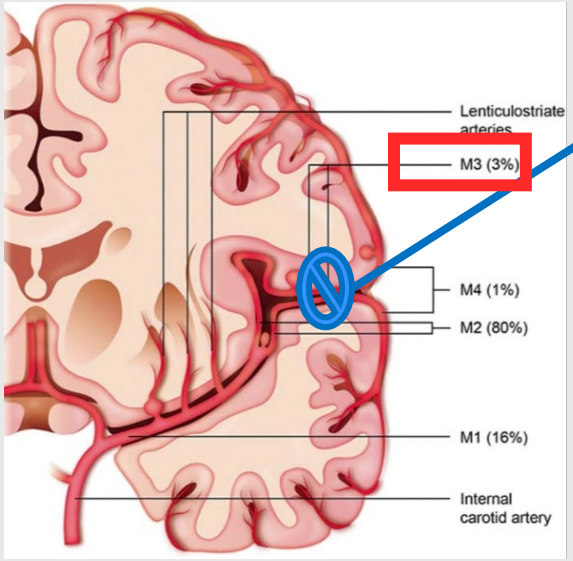
K_D (M)	k_{on} (1/Ms)	k_{dis} (1/s)	Full R^2
3.69E-10	8.62E+04	3.18E-05	0.998



Corti et al. (2022) Syndecan-2 selectively regulates VEGF-induced vascular permeability. PMID: 36212522

THERAPEUTIC EFFECT OF SDC2 ANTIBODY IN NON-HUMAN PRIMATE MODEL OF ISCHEMIC STROKE

Left Hemisphere



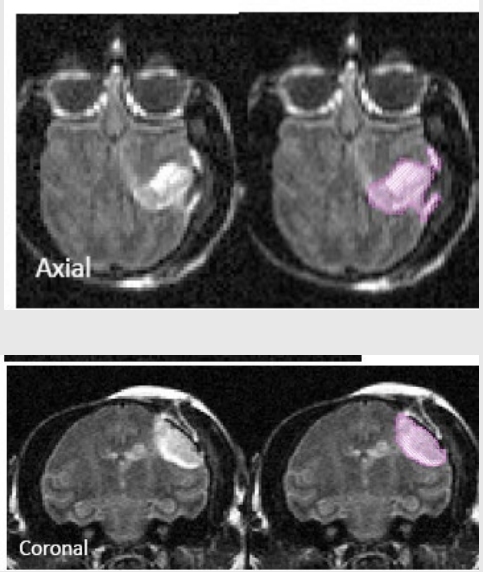
Brasiliense et at. (2017) Evolution of Middle Cerebral Artery Aneurysm Treatment: The Role of Microsurgery in the Endovascular Era—Part II. DOI: 10.1097/01.CNE.0000513125.86431.b8

Occlusion of the M3 branch of MCA with an aneurysm clip (3 hours ischemia)

Reperfusion followed by immediate I.V injection:
Group 1. Vehicle
Group 2. Sdc2 mAb (10mg/kg)

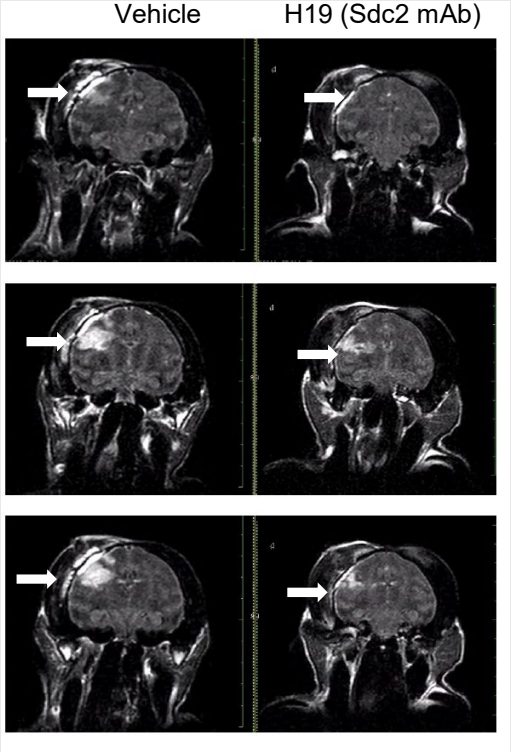
MRI scans at 24 and 72hrs

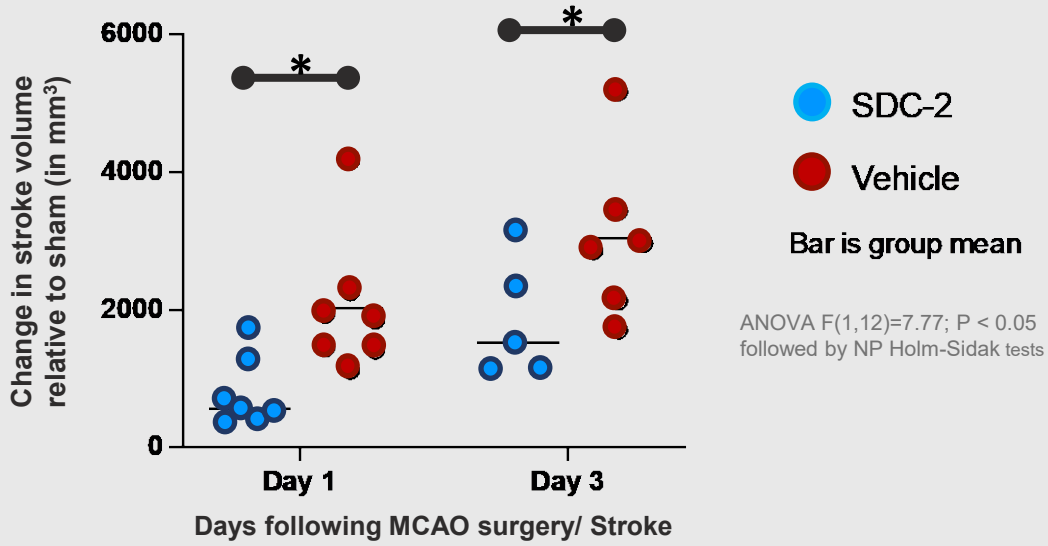
Quantification of infarct size using 2D FLAIR sequences in each plane by AMIRA software



MRI analysis of Stroke Infarct Volume (day 1 AND 3 pp, 2D FLAIR)

A single i.v. bolus of anti-sdc2 blocking antibody stroke induction reduces infarct volume by 60% (day 1) and 50-60% (day 3) as quantified by MRI





INNOVATION AND EFFECTIVENESS OF ANTI-SDC2 ANTIBODY FOR TREATMENT OF ISCHEMIC STROKE

- No safety issues or adverse side-effect were observed in extensive use in both mouse and non-human primate models
- A single i.v. injection leads to 50-60% stroke size reduction and edema formation at day 1 and day 3 post-MCA occlusion
- Therapeutic window is longer than current treatment options (up to 24hrs or more)
- It can be also combined with other treatments (e.g. TPA) without interfering in their mechanism of action
- Potentially reduce the risk of hemorrhagic transformation

THANK YOU

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