#ISC24

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DELAYED THERAPY WITH HUMANIZED ANTI-SDC2 MAB PREVENTS FORMATION OF VASOGENIC EDEMA AND PROMOTES NEUROPROTECTION IN NON-HUMAN PRIMATES WITH ISCHEMIC STROKE

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

Delayed Therapy With Humanized Anti-Sdc2 mAb Prevents Formation Of Vasogenic Edema And Promotes Neuroprotection In Non-human Primates With Ischemic Stroke Therapy With Humanized Anti-sdc2

Federico Corti, PhD

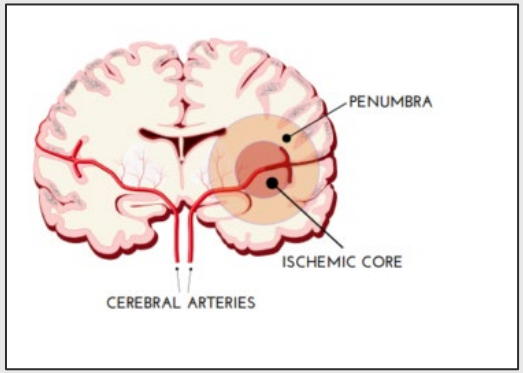
FINANCIAL DISCLOSURE:

Grant/Research Support: VST Bio, Corp., 4653 Carmel Mountain Road, St 308, PMB 1015, San Diego, CA 92130, USA

Federico Corti, PhD and Michael Simons, MD

Cofounders of VST Bio, Corp.

BBB DISRUPTION IN ISCHEMIC STROKE



Reduced BBB integrity

Vasogenic edema

VEGF-A
(Vascular Endothelial Growth Factor A)

ISCHEMIC AND INFLAMMATORY CELLS

Not blocked by glyburide or ion channel modulators

Key Facts:

- An influx of a protein-rich extravasate inside the brain extracellular spaces
- Promotes neurotoxicity and neuroinflammation
- Accelerate the loss of the penumbra
- Develops in few hours and keep increasing over days

VASOGENIC EDEMA IS ASSOCIATED WITH INFARCT PROGRESSION OVER AT LEAST ONE WEEK FROM THE INITIAL ISCHEMIC STROKE

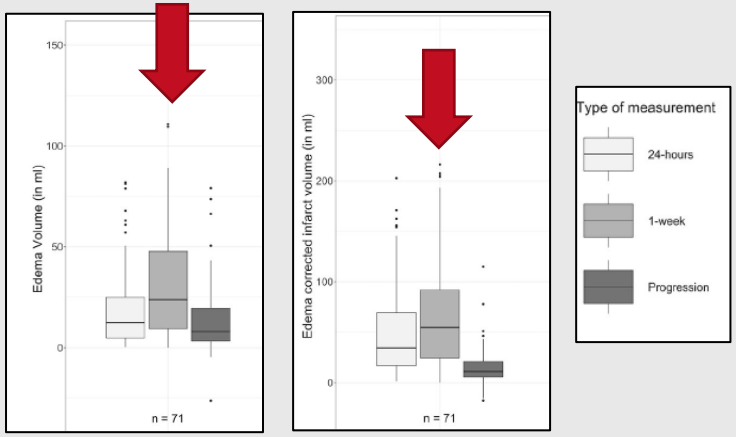
› Front Neurol. 2021 Jul 20:12:705221. doi: 10.3389/fneur.2021.705221. eCollection 2021.

The Role of Edema in Subacute Lesion Progression After Treatment of Acute Ischemic Stroke

Praneeta Konduri [1 2], Katinka van Kranendonk [2], Anna Boers [1 3], Kilian Treurniet [2 4], Olvert Berkhemer [2 5 6], Albert J Yoo [7], Wim van Zwam [8], Robert van Oostenbrugge [9], Aad van der Lugt [6], Diederik Dippel [5], Yvo Roos [10], Joost Bot [11], Charles Majoie [2], Henk Marquering [1 2];
MR CLEAN Trial Investigators (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)

Konduri et al., Front Neurol. (2021)

- 187 patients from MR CLEAN trial (Netherlands, 2010-2014) with high-quality non-contrast CT at 24h and 1 week
- CT densitometry was used to calculated total ischemic lesion volume, edema volume and edema-corrected infarct volume



Patients without successful recanalization

Vasogenic edema contributes to infarct progression and offers a long window of therapeutic opportunity

INHIBITION OF EDEMA IS A STRONGER MEDIATOR OF RECANALIZATION BENEFITS COMPARED TO PENUMBRA SALVAGE

› Ann Neurol. 2023 Sep 19. doi: 10.1002/ana.26802. Online ahead of print.

Edema Reduction versus Penumbra Salvage: Investigating Treatment Effects of Mechanical Thrombectomy in Ischemic Stroke

Gabriel Broocks [1], Andre Kemmling [2], Helge Kniep [1], Lukas Meyer [1], Tobias D Faizy [1], Uta Hanning [1], Leander D Rimmele [3], Susan Klapproth [1], Gerhard Schön [4], Kamil Zeleňák [5], Jens Fiehler [1], Rosalie McDonough [1 6]

Affiliations + expand

PMID: 37726933 DOI: 10.1002/ana.26802

Brooks et al., Ann Neurol. (2023)

- 428 patients (local data registry, 2015-2021) with LVO and successful recanalization
- Primary outcome was functional independence at day 90 with modified Rankin Scale (mRS)

TABLE 4. Mediation Analysis

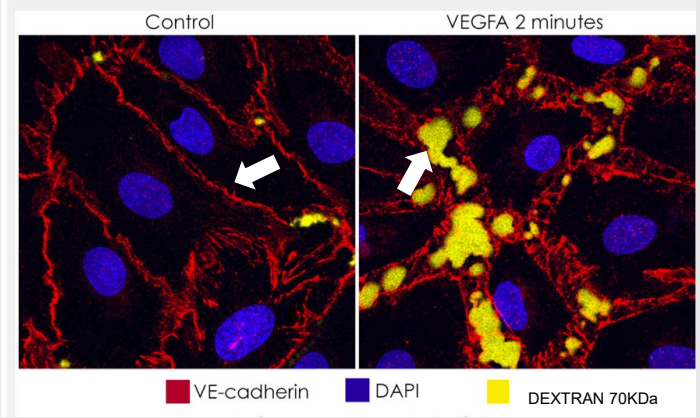
	Outcome: 90-Day mRS; Treatment: mTICI = 2b-3 vs < 2b; Mediator: ΔNWU; Estimate (95% CI)	*p*	Outcome: 90-Day mRS; Treatment: mTICI = 2b–3 vs. < 2b; Mediator: PSV; Estimate (95% CI)	*p*
Total effect	0.93 (0.58–1.28)	<0.001	1.05 (0.71–1.38)	<0.001
Direct effect	0.32 (0.29–0.34)	<0.001	0.82 (0.48–1.15)	<0.001
Effect mediated	0.62 (0.38–0.85)	<0.001	0.22 (0.12–0.33)	<0.001
Total effect mediated, %	Indirect effect/total effect	<0.001	Indirect effect/total effect	<0.001
	0.62/0.32 = 0.66		0.22/0.82 = 0.28	

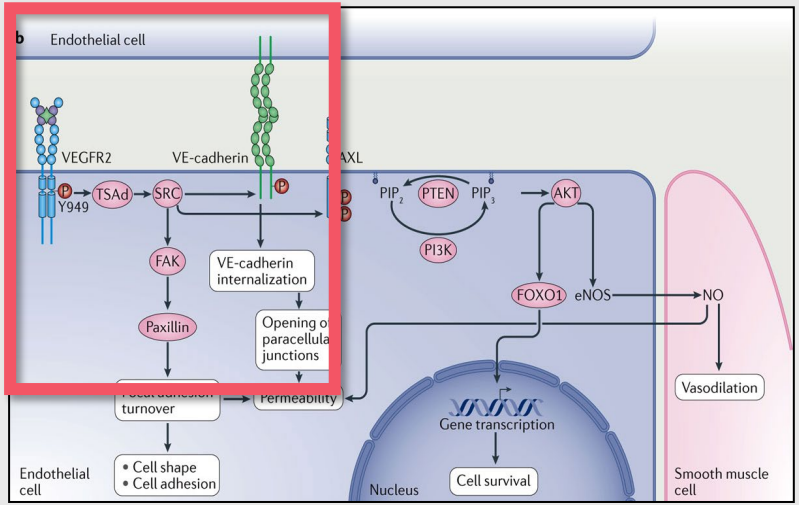
Abbreviations: CI = confidence interval; mRS = ...lified Rankin Scale; mTICI = modified Thrombolysis in C...bral Infarctions; NWU = net water uptake; PSV = penumbra salvage volume.

Mediation analysis revealed that clinical benefit of recanalization (at day 90) are mostly mediated by edema reduction (66%) vs penumbra salvage (22%)

VEGF-A IS A MAJOR DRIVER OF THE BBB DISRUPTION

VEGF-A level strongly increases in ischemic stroke and promotes BBB disruption (that leads to increased vascular leakage in the brain)





Simons et al. (2016) Nature Reviews Molecular Cell Biology *Mechanisms and regulation of endothelial VEGF receptor signalling.*

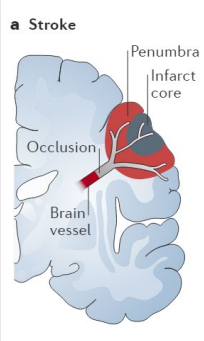
Endothelial cells

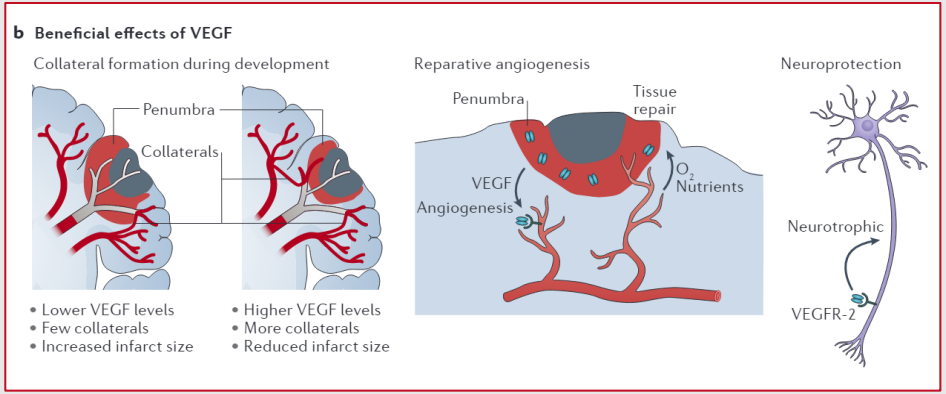
Disruption of endothelial cells monolayer

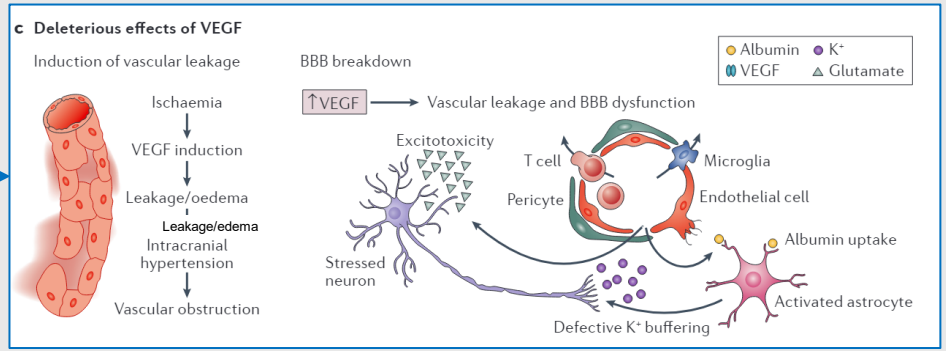
Claesson-Welsh at al. Trends in Molecular Medicine (2020) *Permeability of the Endothelial Barrier: Identifying and Reconciling Controversies.*

INHIBITION OF VEGF-A ACTIVITY IN ISCHEMIC STROKE

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







Issues with total VEGF-A inhibition

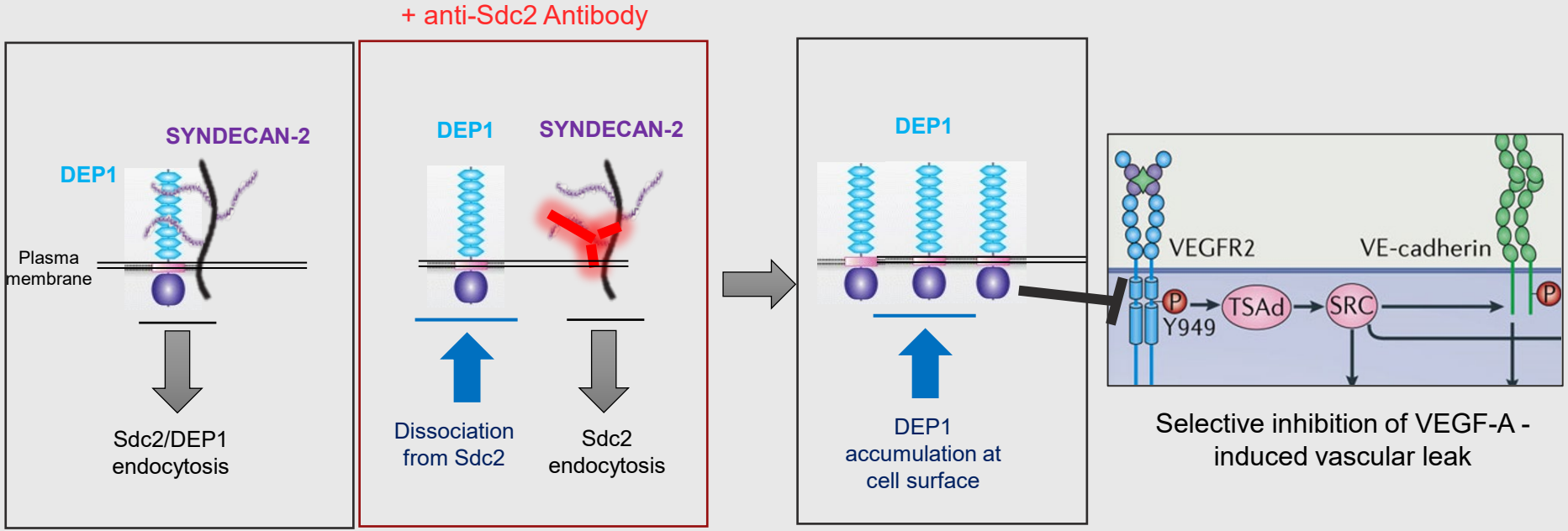
- ✓ Loss of neuroprotection and new blood vessel formation (angiogenesis)
- ✓ Loss of anti-apoptosis/pro-survival effects
- ✓ Reduction in endothelial viability

Benefits of selective VEGF-A inhibition

- ✓ 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) Nature Reviews Neurology. *Vascular endothelial growth factor: a neurovascular target in neurological diseases.*

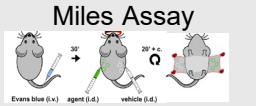
A MECHANISM TO SELECTIVELY BLOCK VEGF-A-INDUCED BBB DISRUPTION AND LEAKAGE

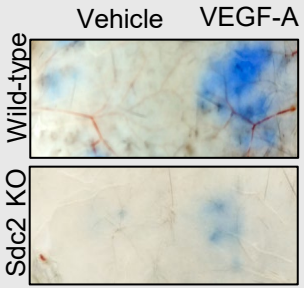


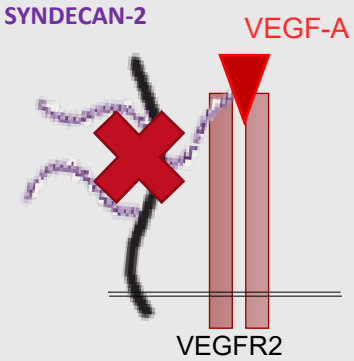
Selective inhibition of VEGF-A - induced vascular leak

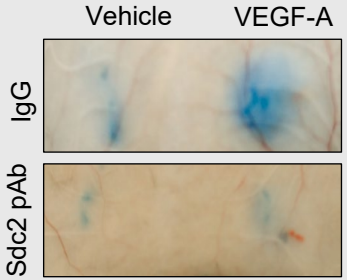
Corti et al. Nature Cardiovascular Research (2022). *Syndecan-2 selectively regulates VEGF-induced vascular permeability.*

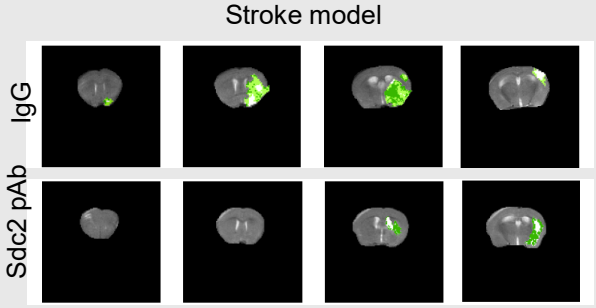
A POLYCLONAL ANTI-SYNDCAN-2 BLOCKING ANTIBODY (Sdc2 pAb) INHIBITS VEGF-A INDUCED VASCULAR LEAK IN MICE

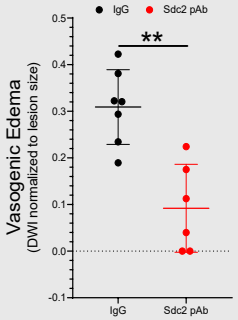








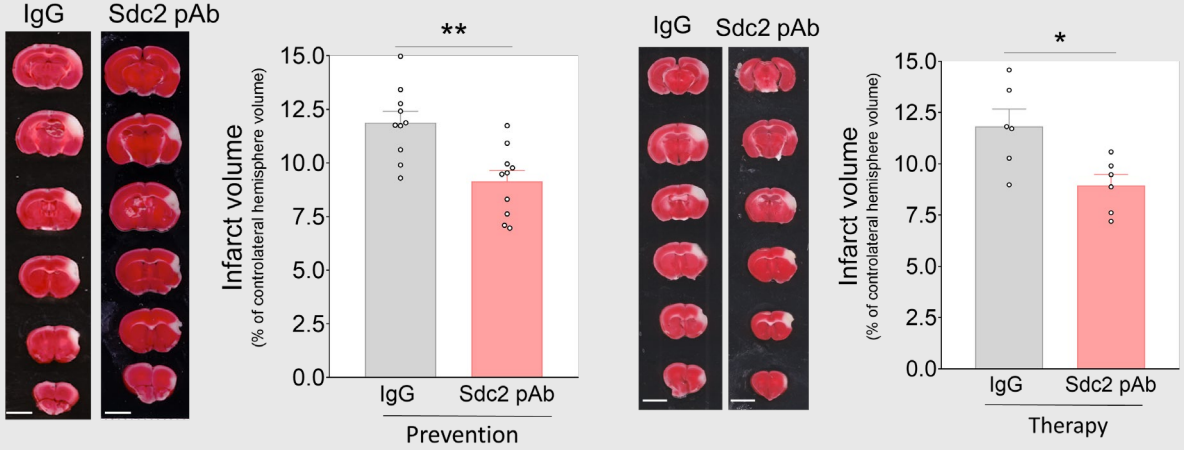




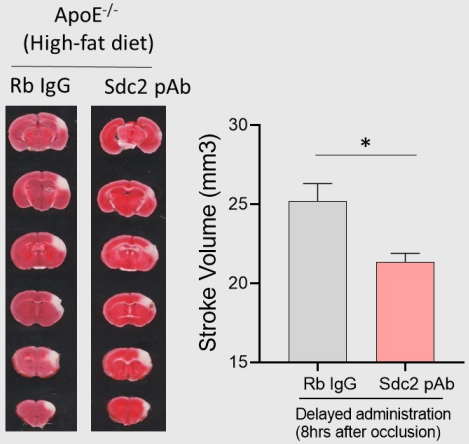
Corti et al. Nature Communications (2019). *N-terminal syndecan-2 domain selectively enhances 6-O heparan sulfate chains sulfation and promotes VEGFA165-dependent neovascularization*

Corti et al. Nature Cardiovascular Research (2022). *Syndecan-2 selectively regulates VEGF-induced vascular permeability.*

Sdc2 pAb PROMOTES NEUROPROTECTION IN ISCHEMIC STROKE MODELS WITH NO-REPERFUSION AND DELAYED THERAPY



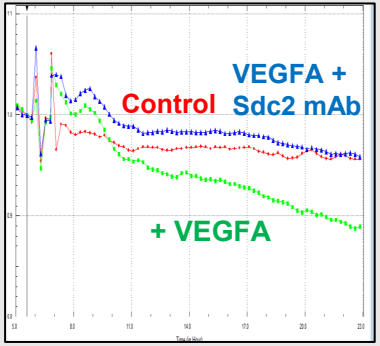
Corti et al. Nature Cardiovascular Research (2022).

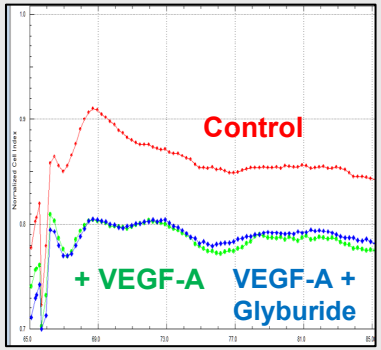


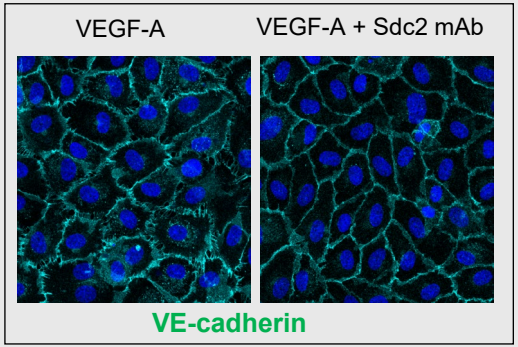
*TTC staining after 72hrs of distal MCA occlusion

Unpublished

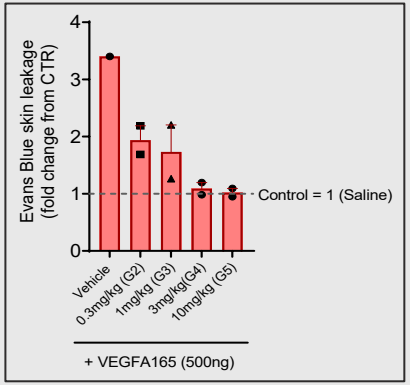
DEVELOPMENT OF A MONOCLONAL ANTI-HUMAN SDC2 ANTIBODY (Sdc2 mAb) THAT SELECTIVELY BLOCKS VEGF-A-INDUCED BBB DISRUPTION







Miles Assay



In vitro endothelial integrity (TEER analysis)

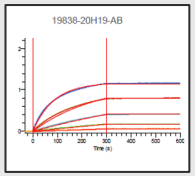
Additional *in vitro* characterization

Early development

Non-Human Primate studies

Hybridoma campaign against human Sdc2 (50 clones identified)

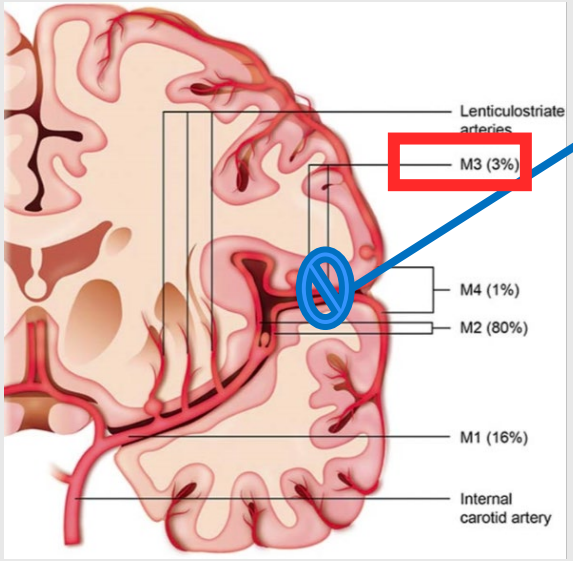
Binding Affinity (nanomolar Kd)



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

Ischemic Stroke in NHP

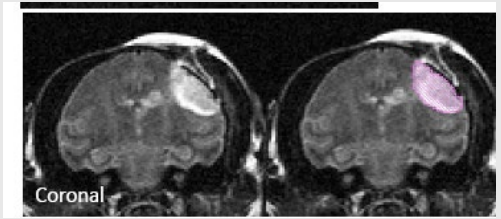
THERAPEUTIC EFFECT OF HUMAN SDC2 mAb IN NON-HUMAN PRIMATE MODEL OF ISCHEMIC STROKE



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 – 3 hours post occlusion (early)
Group 3. Sdc2 mAb – 6 hours post occlusion (delayed)

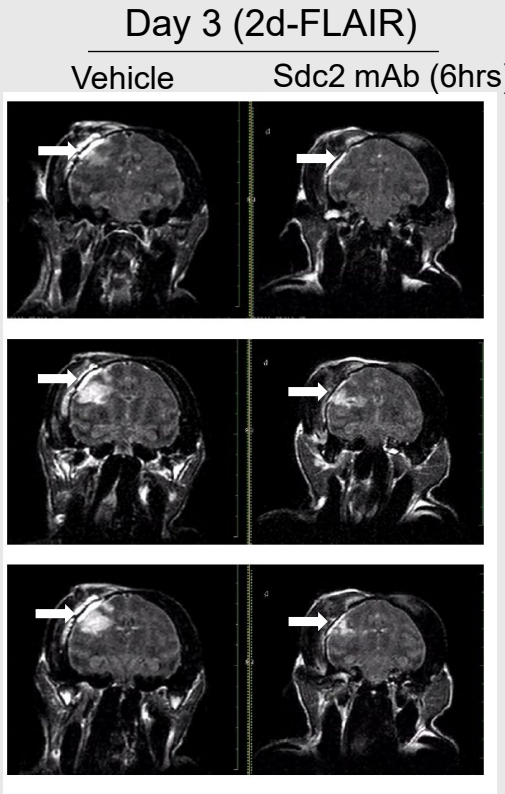
MRI scans (24 and 72hrs)

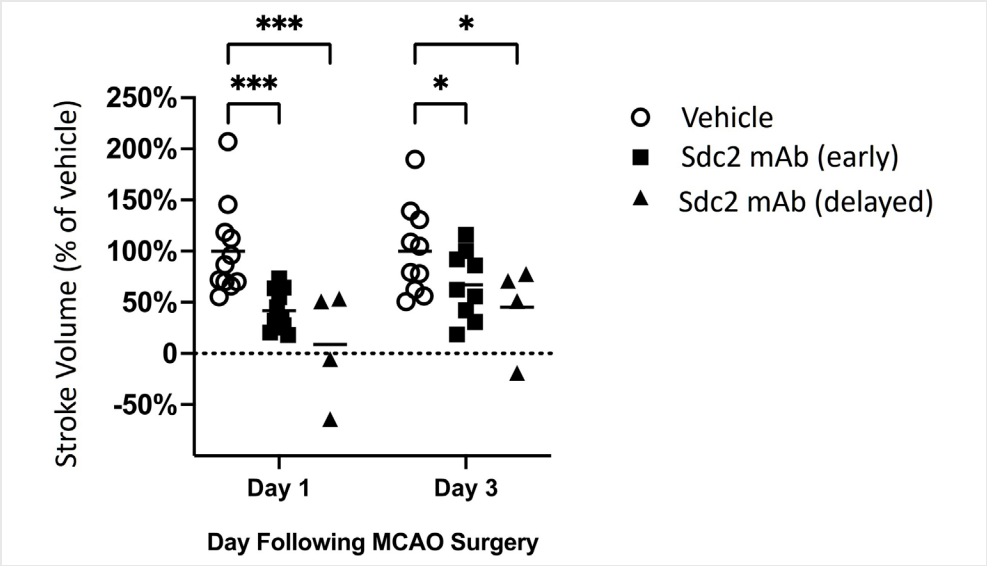


Brasiliense et at. (2017)
DOI: 10.1097/01.CNE.0000513125.86431.b8

MRI ANALYSIS OF TOTAL STROKE VOLUME

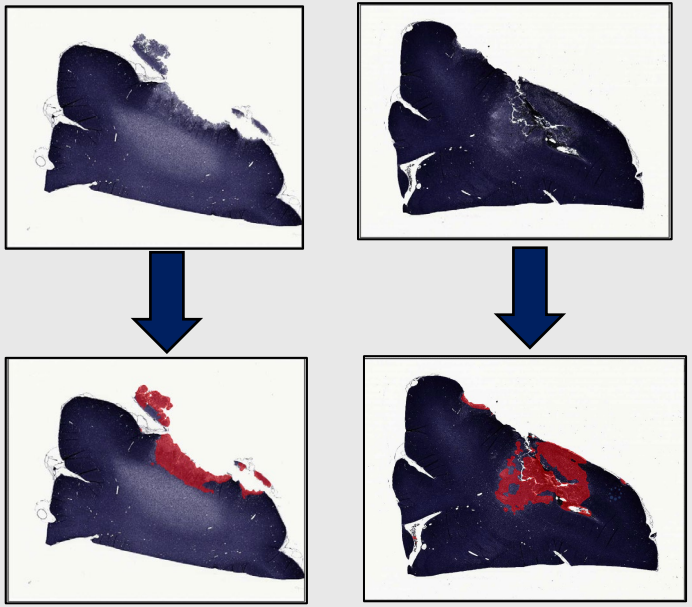
A single I.V. bolus of Sdc2 mAb significantly reduces total infarct volume in both early and delayed treatment groups





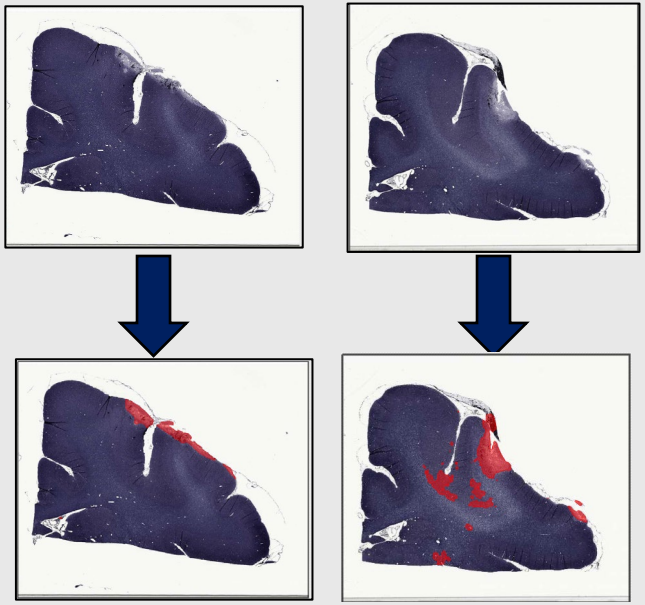
AI-TRAINED IMAGE ANALYSIS REVEALED A REDUCTION OF NECROTIC INFARCT AREA IN ANIMALS TREATED WITH SDC2 mAb

Vehicle (DAY 3, ICS staining)



necrotic core in red

Sdc2 mAb (DAY 3, ICS staining)



necrotic core in red

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

- No adverse side-effects were observed in extensive use in both mouse and non-human primate models
- A single I.V. injection led to significant stroke size reduction and edema formation at day 1 and day 3 post-occlusion
- Sdc2 mAb does not need to cross BBB since it directly targets the endothelium
- Therapeutic window is longer than current treatment options (up to 24hrs or more)
- Sdc2 mAb may combined with other treatments (e.g. TPA) without interfering with their mechanism of action
- Sdc2 potentially reduces the risk of hemorrhagic transformation

THANK YOU

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