VST BIO CORPORATION
Vascular Therapeutics

Modulation of Vasogenic Edema

10/20/23

VST-Bio Overview

First-in-class drugs target novel pathways regulating vascular permeability

- VST-Bio researchers have discovered new pathways that regulate vascular permeability and target them with fully human and humanized monoclonal antibodies
  - These drugs result in reduction of systemic vascular leak, which worsen disease processes in stroke, myocardial infarction, and retinopathies
  - We have completed two primate studies demonstrating safety, 1) dose –response pharmacological activity, and 2) significant reduction of stroke volumes (50-60%)
- We will develop these drugs for cardiovascular diseases such as:
  - Ischemic Stroke- reduce vasogenic edema
  - Hemorrhagic Stroke
  - Acute Myocardial Infarction
- We propose to partner ocular indications:
  - Age-Related Macular Degeneration (AMD)

VST-Bio Board of Directors, Founders, and Key Executives

Michael Simons, MD FACC FAHA
Co-Founder
- RW Berliner Professor of Medicine and Cell Biology, **Yale University**
- Led the first trials of therapeutic angiogenesis in the USA and his basic research discoveries have played an important role in moving the field forward
- Over 270+ peer reviewed publications, PI in over 25 international trials

David Cheresh, MD PhD
Director
- Distinguished Professor and vice chair of research, **University of California**, San Diego
- Previous professor at The **Scripps Research Institute**
- Over 240+ peer reviewed publications
- Initiated a number of Biotech start-ups including TargeGen (later acquired by Sanofi)
- (Fedratinib—Jak2 inhibitor, Vitaxin, Celingitide)

Krisztina Zsebo, PhD
CEO, Co-Founder & Director
- Previous EVP Research and Product Development, **Cell Genesys** and **Connetics**
- Previous **Venture Partner, Enterprise Partners Venture Capital**
- Previous CEO, **Remedyne** and **Celladon**
- Co-founder of three previous start-ups, in healthcare and investment management

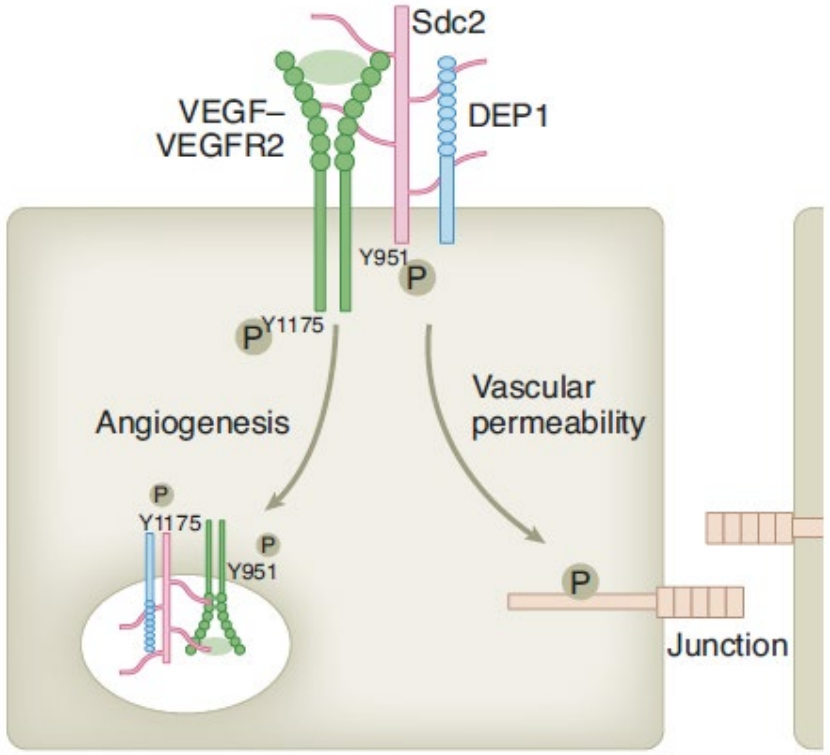
Anthony Ware, MD – Director
Eli Lilly and Company, Indianapolis
- Professor of medicine and molecular pharmacology at **Albert Einstein College of Medicine**
- Chief of cardiology at Montefiore Medical Center, Albert Einstein College of Medicine, New York
- Sen.VP Product Development, Lilly Bio-Medicines, **Eli Lilly and Company**, involved in the approval of Taltz®, Olumiant®, Cymbalta®, Cialis®, Effient® and Trulicity®.

Barbara Thorne, PhD
CMC Development Consultant
- 30+ years experience in drug and biologics development
- Exec. Director, process & Product Development, **Celladon**
- Sr. Director, Process Development, **Targeted Genetics Corp**
- Sr. Research Investigator, **Bristol Meyers Squibb**

Rebecque Laba
VP Finance & Administration
- > 25 yrs experience in biotechnology
- Previous VP Finance and Corporate Operations, **Celladon Corp**
- Previous VP Finance & operations, **Arcturus Therapeutics**
- Previous COO & CFO, **Fremon Scientific**

Controlling Vascular Permeability Is a Significant Unmet Need

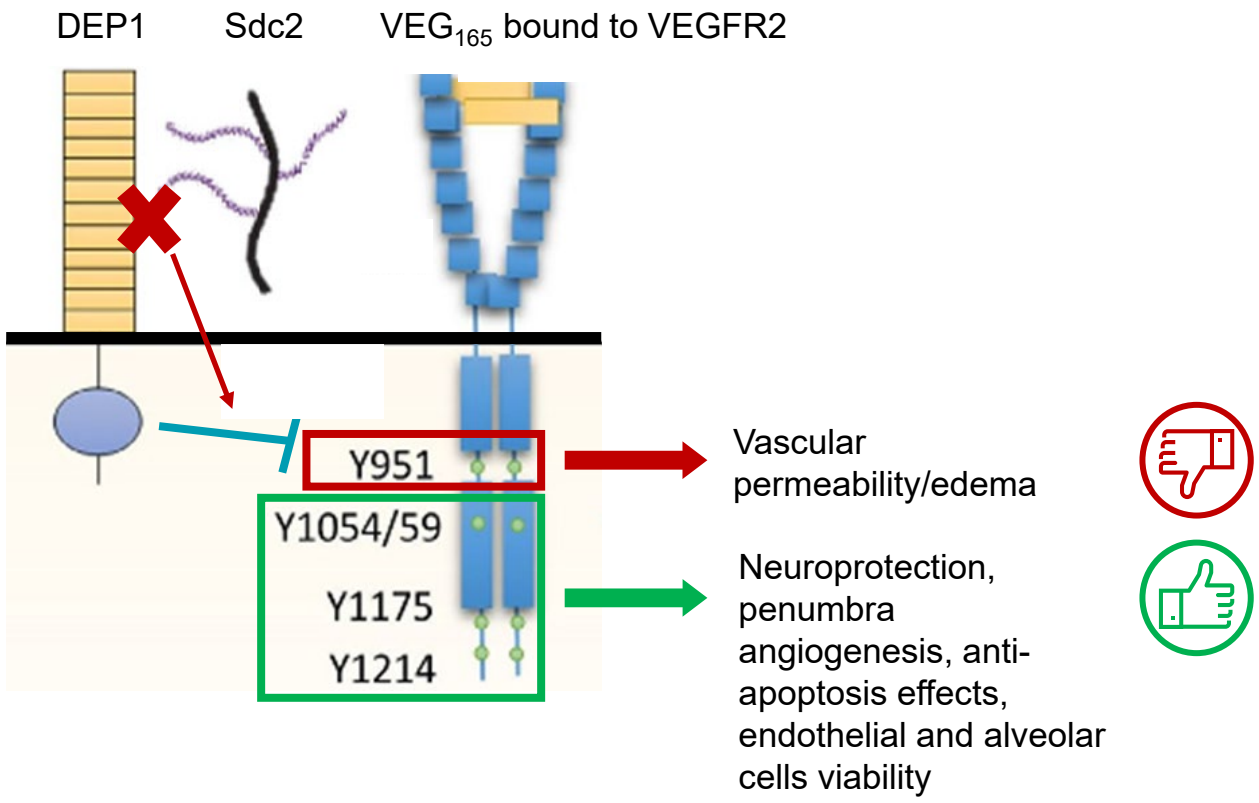
- VEGF is increased in response to inflammation or hypoxia and induces vascular leak (edema)
- Acute or persistent leakage of macromolecules in stroke, myocardial infarction, retinopathies and cancer **worsen the disease process***
- Agents that completely shut down VEGF–VEGFR2 signaling eventually cause endothelial death, loss of vascular supply, and disease progression
- Pan-inhibition of VEGF/VEGFR2 is associated with hypertension, neutropenia, and bleeding
- ***Selective blocking of vascular leak is needed***



*Kim, I. D., Cave, J. W. & Cho, S. *Stroke* **52**, 2637–2648 (2021).

Blocking DEP1 Binding Site of Sdc2 with Monoclonal Antibodies

Deactivates VEGFR2 Y951-Permeability Pathway but Not the Beneficial Effects of VEGF Signaling



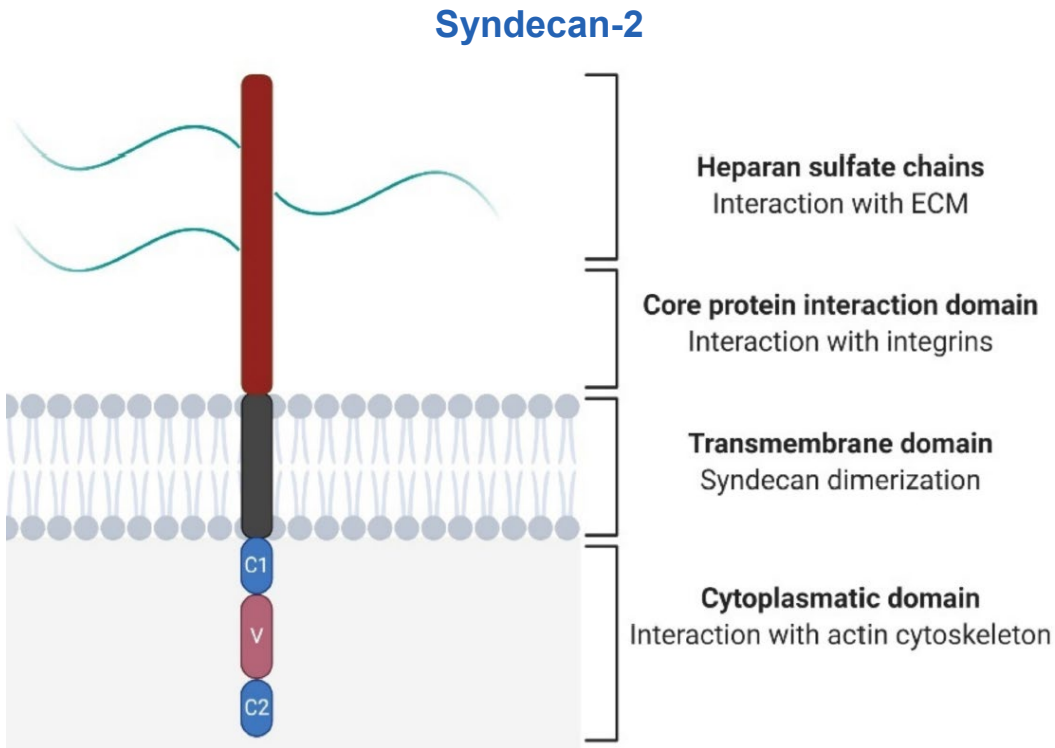
- VEGF during injuries such as stroke and myocardial infarction have a biphasic effect:
  - In the acute phase, VEGF is detrimental, causing increased permeability
  - In the recovery phase the pro-angiogenic effects of VEGF promote post-stroke recovery.

- Therefore, specifically targeting Y951 phosphorylation and suppressing pathological vessel leakage without harming the pro-angiogenic functions of VEGF is highly desirable.

Li et.al., Nat Commun. 2016 Mar 23;7:11017; Corti et al. (2022). PMID: 36212522

Targeting Syndecan-2 Reduces Vascular Permeability Without Inhibiting the Positive Effects of VEGF

- Syndecan-2 is a heparan sulfate proteoglycan which forms a ternary Sdc2-VEGFA-VEGFR2 complex and enhances VEGFR2 activation
- Anti-Sdc2 antibodies:
  - Safely reduce systemic vascular leakage without the negative effects of pan-VEGF inhibition
  - Do not affect the positive activities of VEGF
    - Neuroprotection, penumbra angiogenesis, anti-apoptosis effects, endothelial and alveolar cells viability
  - Reduce inflammatory cell infiltration to sites of injury

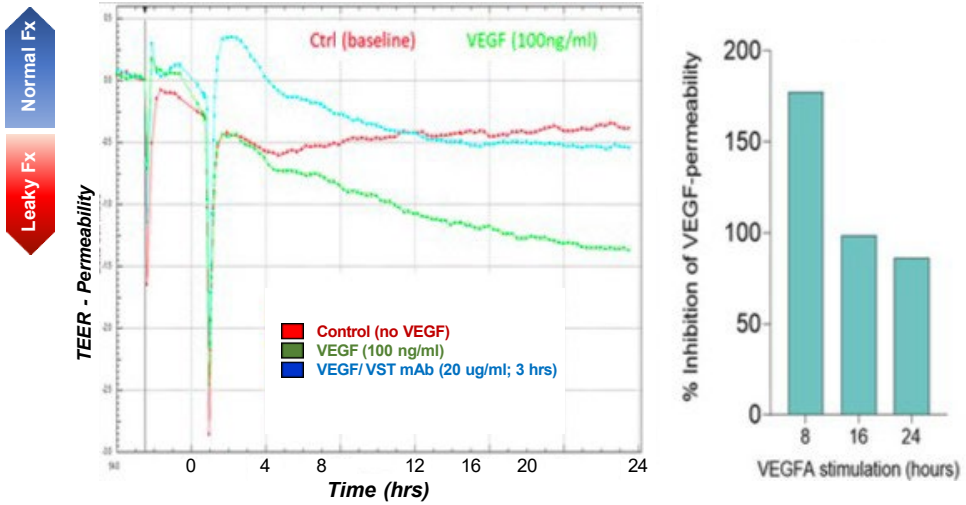


Anti-Sdc 2 mAb Is Able to Block Vascular Permeability

In vitro and *in vivo* endothelial cell permeability testing

In vitro TEER analysis—'Intervention'

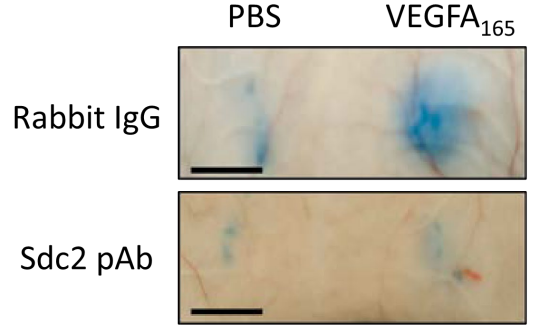
mAb (20 ug/ml) is given 3–40 hrs after VEGF stimulation



In vivo 'Miles Assay'

– iv anti-Sdc2 mAb infusion

– iv Evans Blue/ local sc Injection of VEGF



- TEER: transendothelial electrical resistance
- VST Bio mAb Clones have high affinity for SDC2 extra cellular domain (humanized mAb sub-nanomolar)
- Are able to completely reverse VEGF-induced permeability
- Normalized permeability is maintained for at least 24 hours (after VEGF stimulation)
- *In vitro* permeability function (in endothelial cells; TEER) correlates with *in vivo* skin permeability testing (Miles test)

Safety & Efficacy of VST-Bio mAb in Non-human Primate Model

- Non-human primate model (male Macaca Fascicularis, 2.4 kg ±0.05)
- Single-dose escalating study of anti-human Sdc2 mAb up to 10 mg/kg (cyn IgG4)
- Animals were sacrificed at day 1 and 7 post infusion for histological analysis and a Miles Skin Test for Permeability (VEGF-induced Vascular Leakage)
- Blood collection for safety lab analysis at BL, 15m, 1h, 1.5h, 1d, 3d, and 7d
- **Goals:** Safety, tolerability, and dose-effect relation (dose-selection)

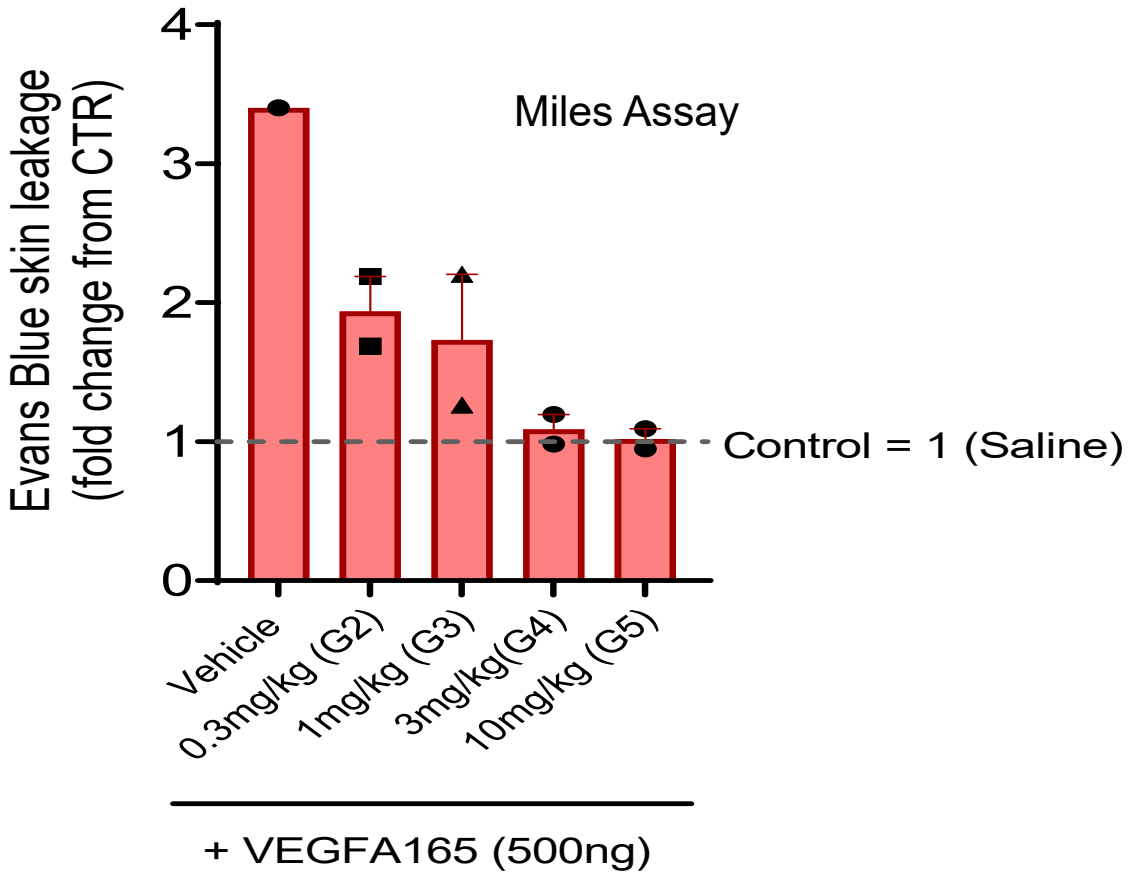
Dose anti-hSdc2 mAb	N
0 mg/kg	2
0.3 mg/kg	4
1.0 mg/kg	4
3.0 mg/kg	4
10.0 mg/kg	4

Safety of VST-Bio mAb in Non-human Primate Model

- Anti-human Sdc2 mAb (up to 10 mg/kg iv bolus) was well tolerated and safe in the non-human primate model, with
  - No mortality
  - No behavioral changes
  - No apparent biochemical or hematological changes
  - Histological analysis showed no changes in brain/liver/kidney/lung/heart/spleen

Pharmacological Activity Demonstrated in Primate Model

- Effective dose-dependent reduction and even normalization of vascular permeability (‘vascular leakage’) at dose of 3–10 mg/kg
- Reduction of VEGF-induced permeability persisted at 7 days follow-up (with 50% reduction)



First Clinical Indication: Stroke

- VEGF drives brain edema: an acute pathological event in stroke that leads to blood-brain barrier disruption, inflammation, ionic dysregulation, hemorrhagic transformation, and increased mortality
- Over 90% of all stroke patients are not eligible for front-line thrombotic therapy and are treated with conservative measurements such as Aspirin and anti-hypertensive therapy, or surgery such as craniotomy
- As edema after stroke lasts for days, we estimate that our therapy will be effective in the 3 days after onset of symptoms, and would be add on therapy to other conservative treatments, capturing a majority of patients
- $31.7B USD addressable market worldwide in 2020**(CAGR 7.8%)

*Kim, I. D., Cave, J. W. & Cho, S. *Stroke* **52**, 2637–2648 (2021); * Fortune Business Insight; ** Emergen Research; *** P Market Research.

Edema Reduction versus Penumbra* Salvage in Stroke

- Reperfusion of blocked arteries in the brain via thrombolytics or mechanical thrombectomy improves functional outcome
- Broocks et. al.# quantitatively assessed how the effect of vessel recanalization on clinical outcome is mediated by edema reduction versus penumbra salvage
- Compared to penumbra salvage, edema reduction was a stronger mediator of the effect of recanalization on functional outcome.
  - ***Sixty-six percent of the relationship between recanalization and functional outcome could be explained by treatment-induced edema reduction, whereas 22% was mediated by penumbra salvage volume ($p < 0.0001$).***

*Perfused brain tissue around the necrotic core which has the capacity to recover and be salvaged if perfusion is improved rapidly.

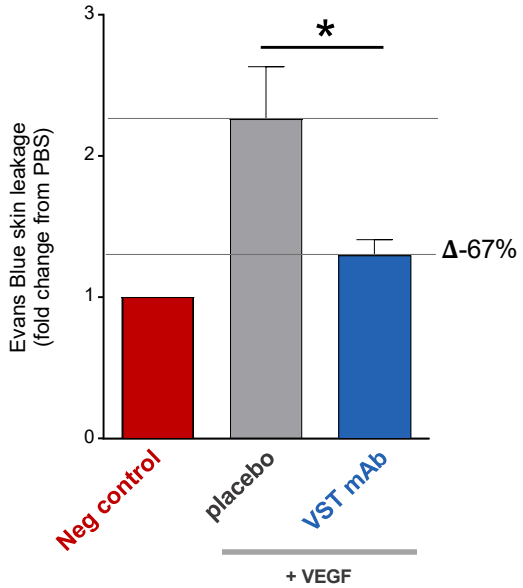
Edema Reduction versus Penumbra Salvage: Investigating Treatment Effects of Mechanical Thrombectomy in Ischemic Stroke 2023 Sep 19. doi: 10.1002/ana.26802 PMID: 37726933

Sdc2-blocking Antibody Reduces VEGFA-Induced Permeability, Infarct Size, and Survival in Mouse Stroke Model

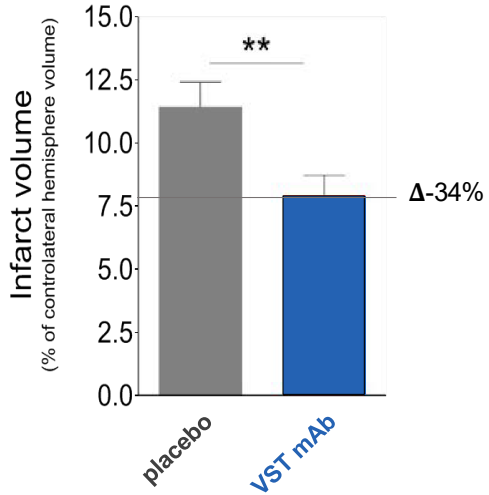
8–12 weeks old B6 mice → IV injection at 4 ug/g
- Control rabbit IgG
- Anti-Sdc2 (RbαMs)

→ Wait 2 hrs. →
- VEGFA-Skin permeability
- Stroke

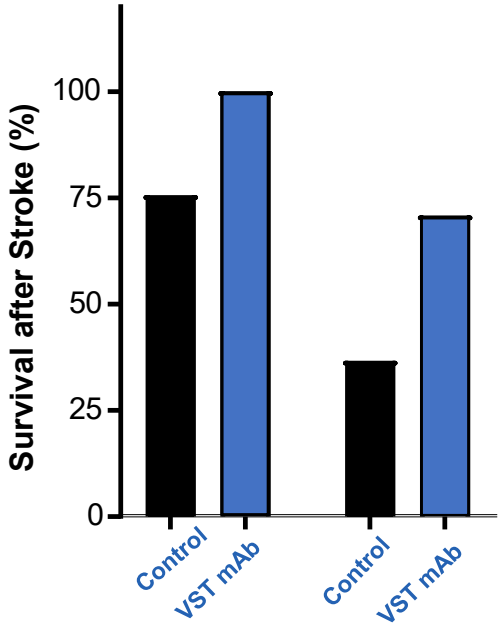
VEGFA-Skin Permeability



Murine Stroke Model

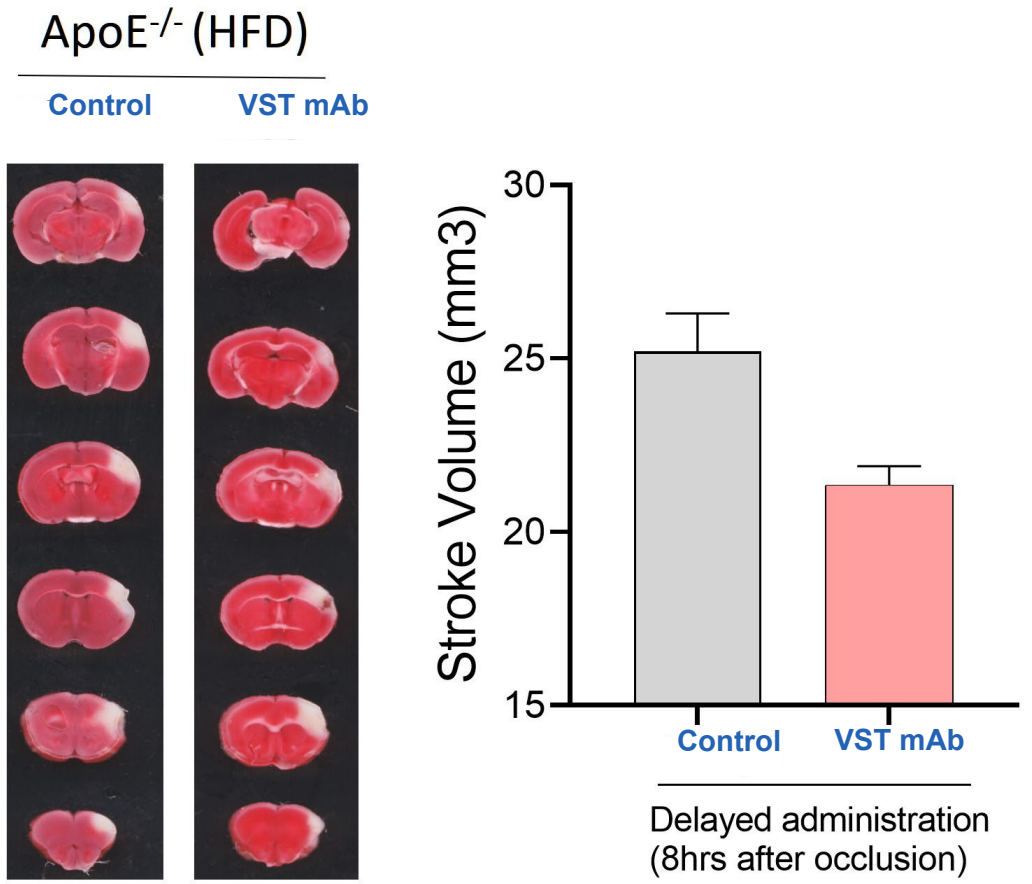


Survival



Corti, Simons and co-workers, Nature CardioVascular Research (2022), 1, pg 518.

Delayed Treatment in Stroke with Aged Atherosclerotic Mice



*TTC staining after 72hrs of distal MCA occlusion

Sdc2-blocking Antibody Reduces VEGFA-Induced Permeability, Infarct Size, and Survival in Primate Stroke Model

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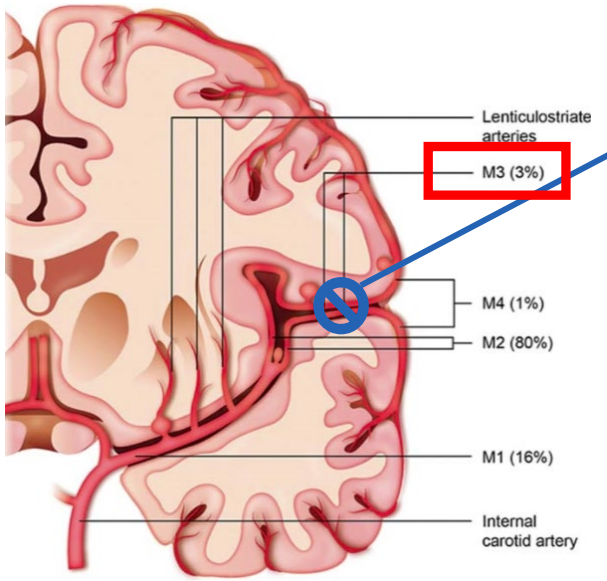
Vascular Therapeutics

Left Hemisphere

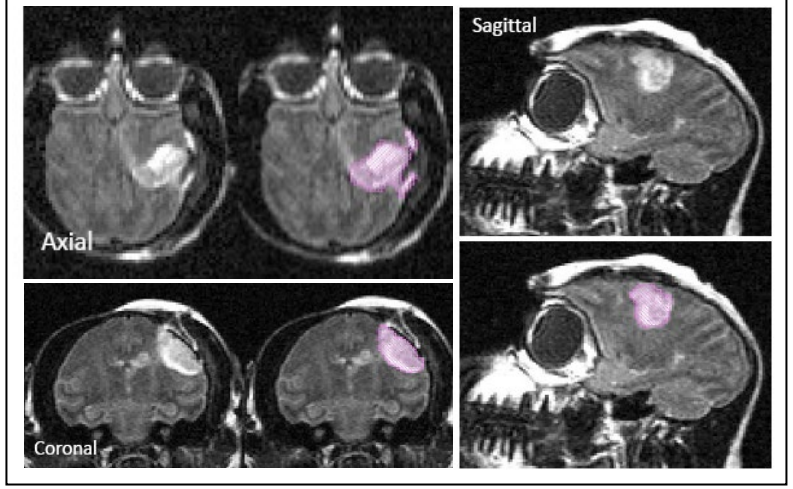


Occlusion of the M3 branch of middle cerebral artery with an aneurysm clip (3 hours ischemia)

Reperfusion followed by immediate I.V injection:
Group 1. Vehicle
Group 2. Sdc2 mAb (10mg/kg)
or Group 3 – Sdc2 mAb (10/mg/kg) 3 hrs. later (6 hrs. after occlusion initiated

MRI Scans at 24 and 72 hours

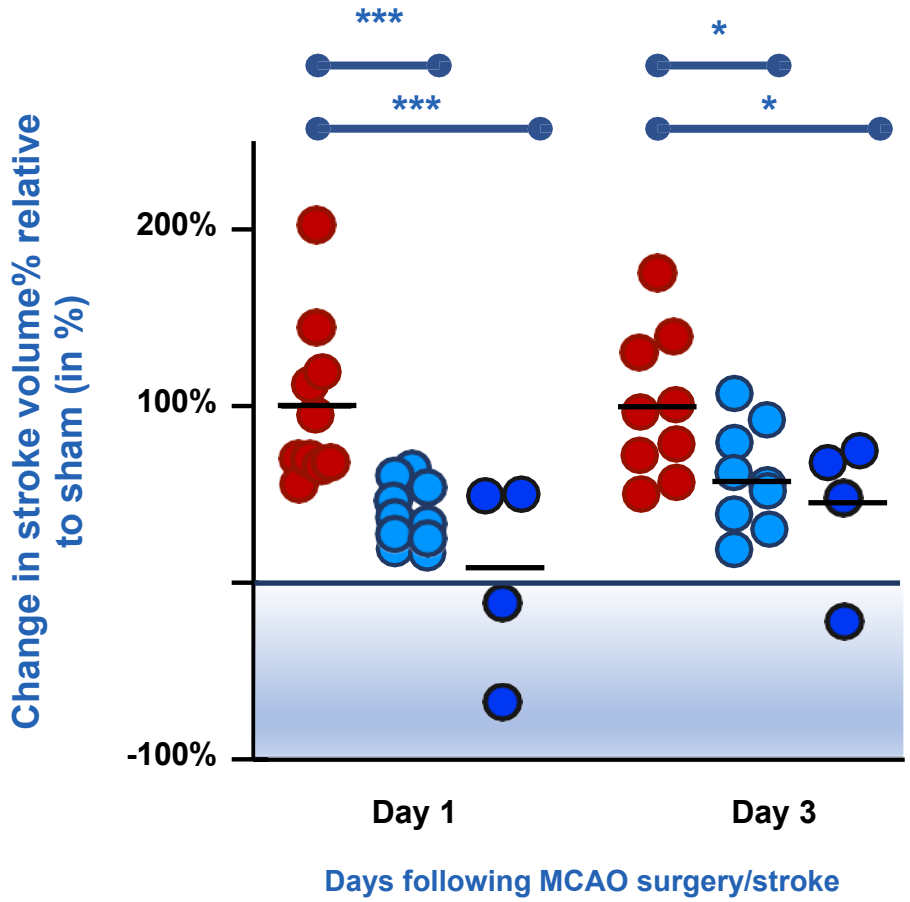
Quantification of infarct size using 2D FLAIR (fluid attenuated inversion recovery)



FLAIR is an advanced magnetic resonance imaging sequence that allows detection of superficial brain lesions.

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.

VB201 Sdc2-blocking Antibody Therapy in Non-Human Primate Stroke Model



Stroke Volume: Percent of Control

- SDC-2, started early (3 h)
- SDC-2, started late (6 h)
- Vehicle

Bar is group mean

Rep. Meas. 2 Way-ANOVA: Tx vs placebo F(2,21)=8,43; P=0.002 followed by NP Holm-Sidak tests

Day 1: early: P=0.0008, late: P=0.0004 Day 3: early: P=0.0401, late: P=0.0401

Composite data: A single iv bolus of anti-sdc2 blocking antibody reduces stroke volume by a remarkable 50–60%, even when the therapy is initiated at 3 or 6 hrs after stroke onset. Conventional SOC therapy (rtPA) is only effective when given <3-4 hrs after start of stroke-related symptoms.

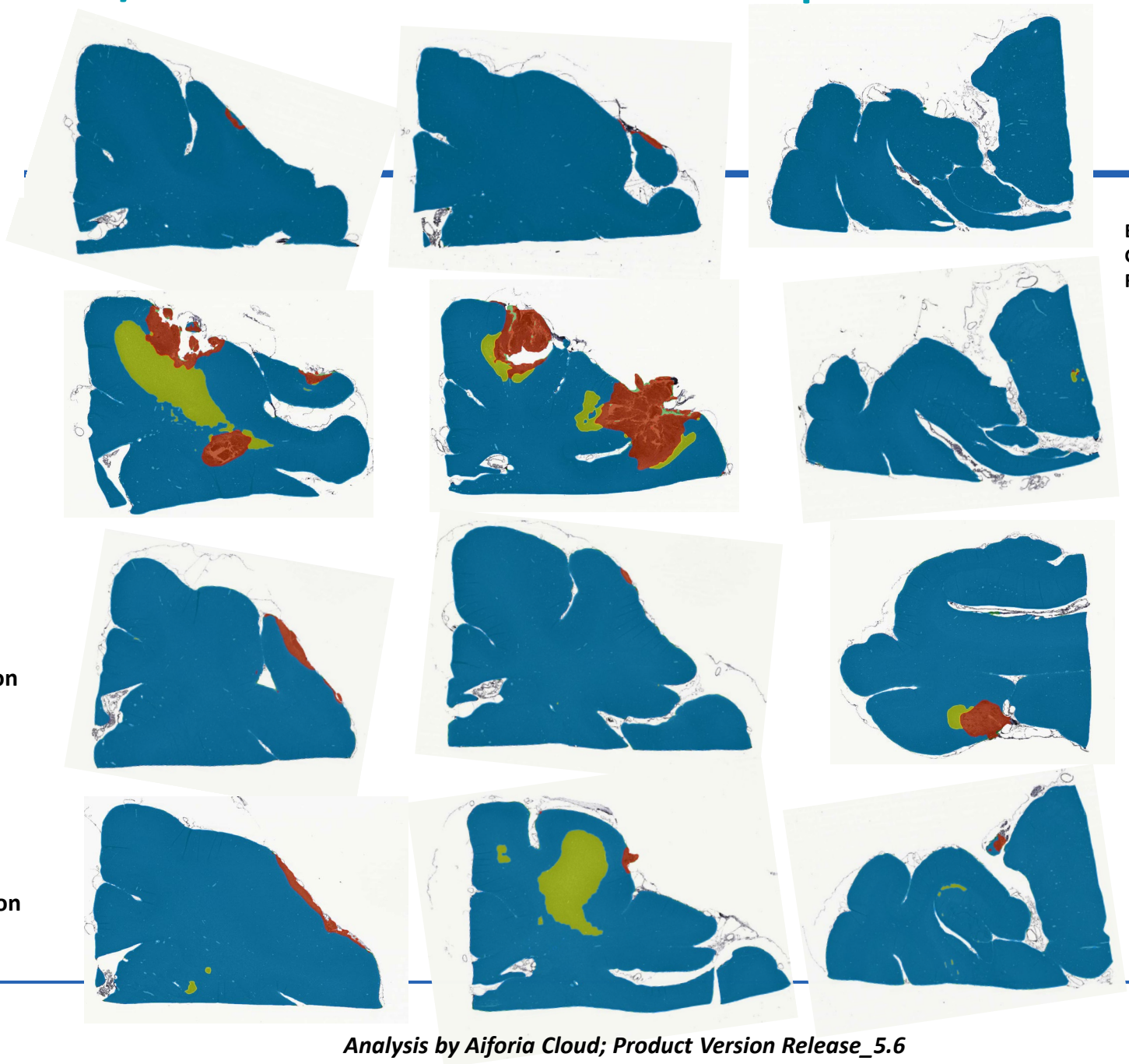
Representative Images Necrosis/Ischemia 3 hrs and 6 hrs Post Reperfusion

Animal E363 - Sham

Animal E357 – Vehicle

Animal E359 – Treatment at 3 hrs post occlusion

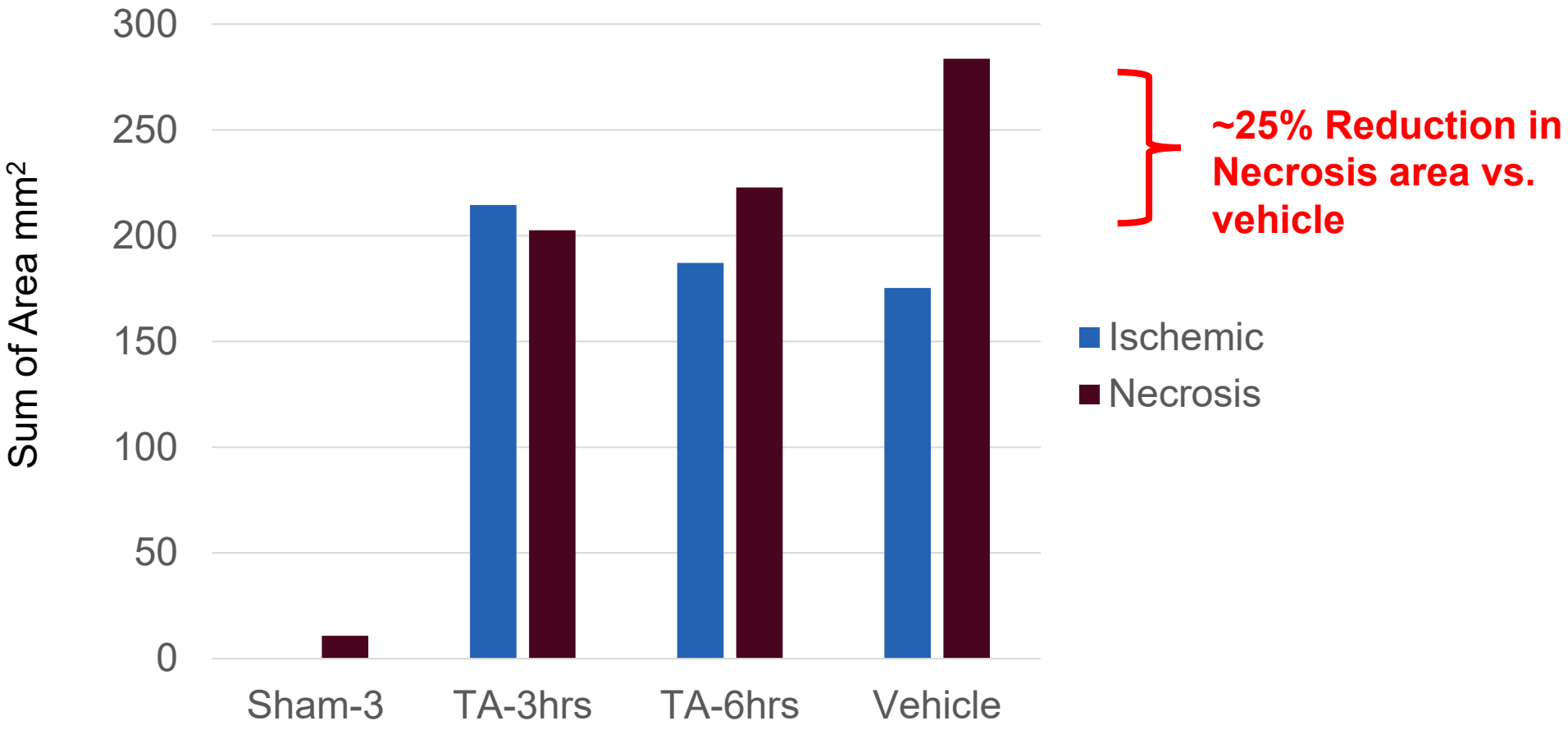
Animal E175 – Treatment at 6 hrs post occlusion



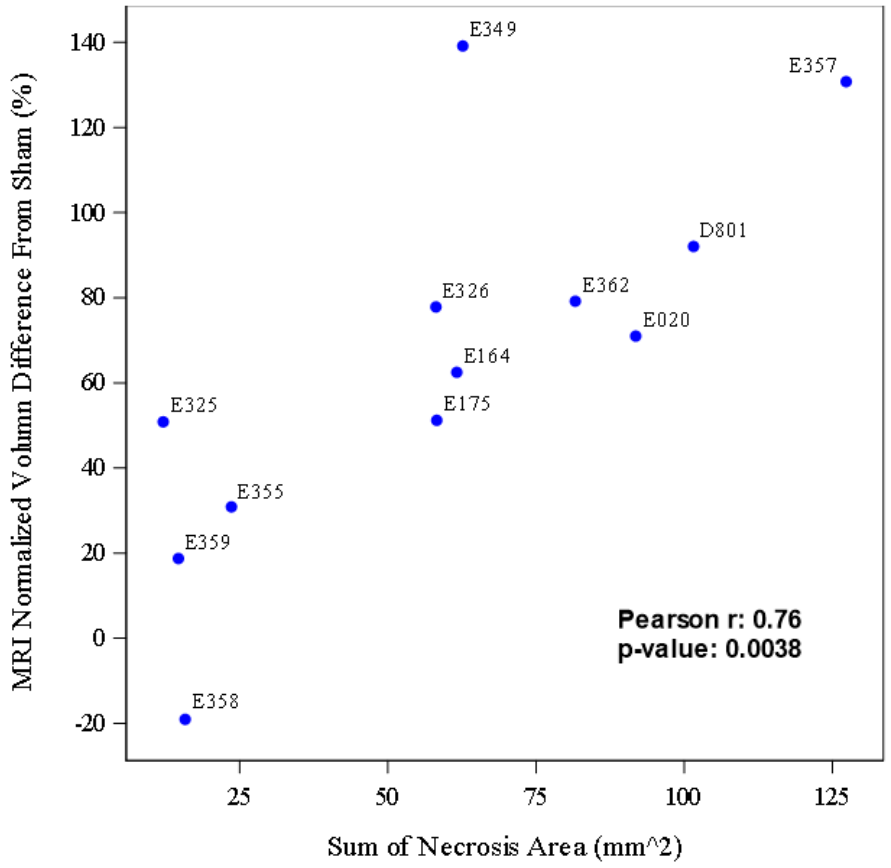
Blue – Normal Tissue
Green – Ischemic Tissue
Red – Necrotic Tissue

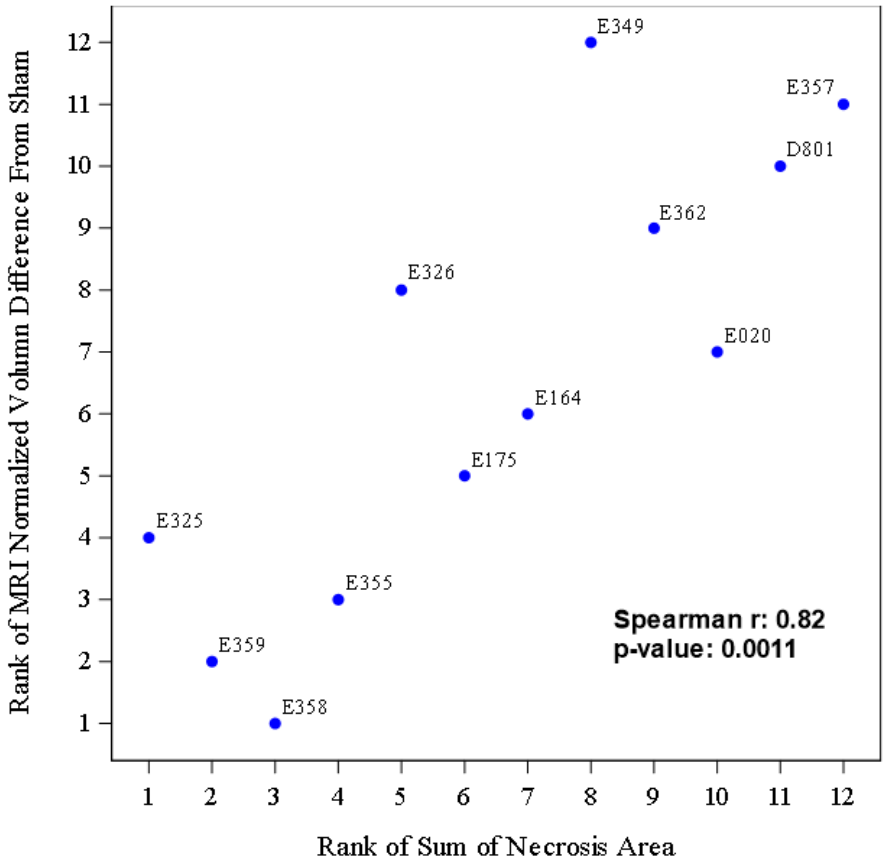
Analysis by Aiforia Cloud; Product Version Release_5.6

Histology of Brains at 3 Days Post MCAO Occlusion



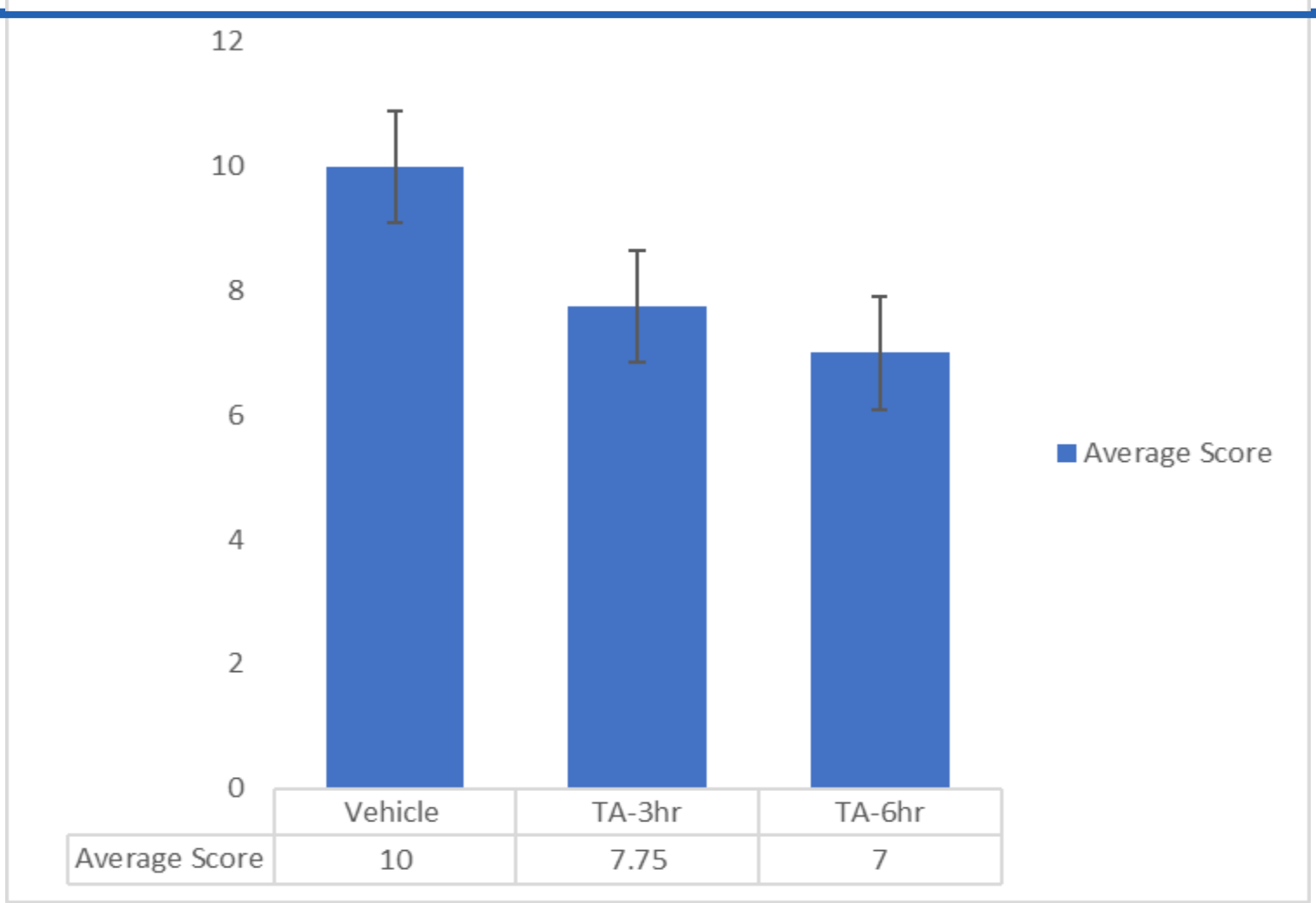
MRI & Histology* Results for Necrotic Area Are Highly Correlated





* Remaining animal histology ongoing and will be available late November ‘23

Cerebral Edema Semi-Quantitative Histopath Score



	Vehicle	TA-3hr	TA-6hr
Average Score	10	7.75	7

Effectiveness of Anti-Sdc2 Antibody for Treatment of Ischemic Stroke

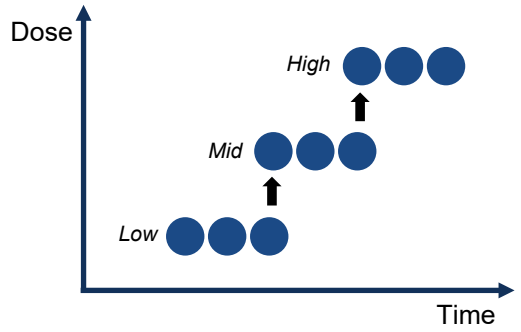
- No safety issues or adverse side effects were observed in extensive use in both mouse and two non-human primate models
- A single i.v. injection leads to 50–60% stroke size reduction and edema formation at Day 1 and Day 3 post-MCA occlusion
- Therapeutic window is longer than current treatment options
- Potentially reduce the risk of hemorrhagic transformation

Early Clinical Development Plan

VB-001: Acute Ischemic Stroke, Phase 1/2 Seamless Design

Phase 1/2 Acute Ischemic Stroke

Single Ascending Dose Lead-In



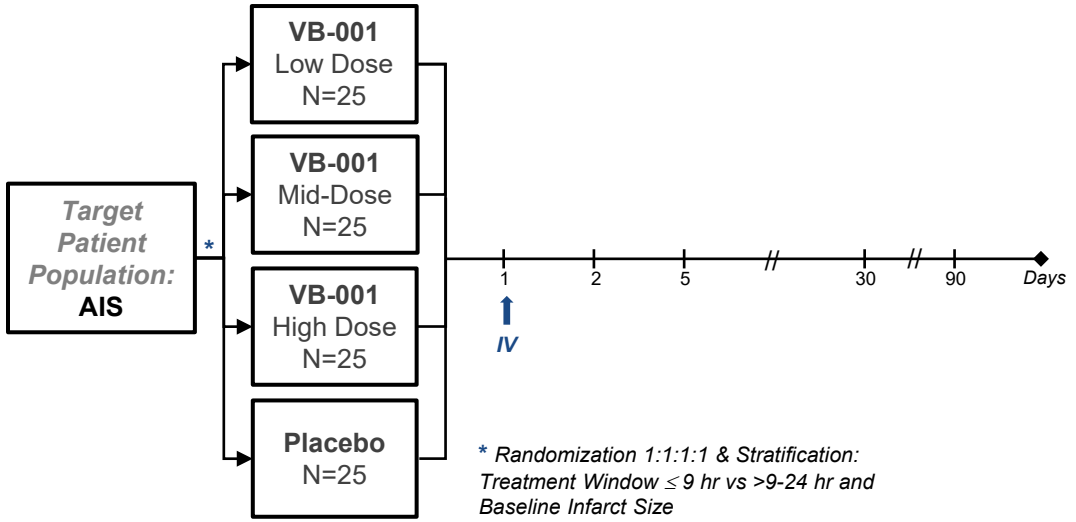
Safety Endpoints
- Incidence, severity & relationship of AEs
- Mortality and final disposition
- Change from baseline in laboratory analytes

Exploratory Efficacy Endpoints
- Change in infarct volume from baseline to Days 2 and 5 as assessed by DW-MRI
- Change in NIHSS, mRS and BI from baseline to Days 2, 5, 30 and 90

Abbreviations: **AEs**, adverse events; **DW-MRI**, diffusion-weighted magnetic resonance imaging; **NIHSS**, National Institute of Health Stroke Score; **mRS**, modified Rankin Scale; **BI**, Barthel Index

Phase 2 Acute Ischemic Stroke

Randomized Controlled Trial, ~18 Centers, 18 Months

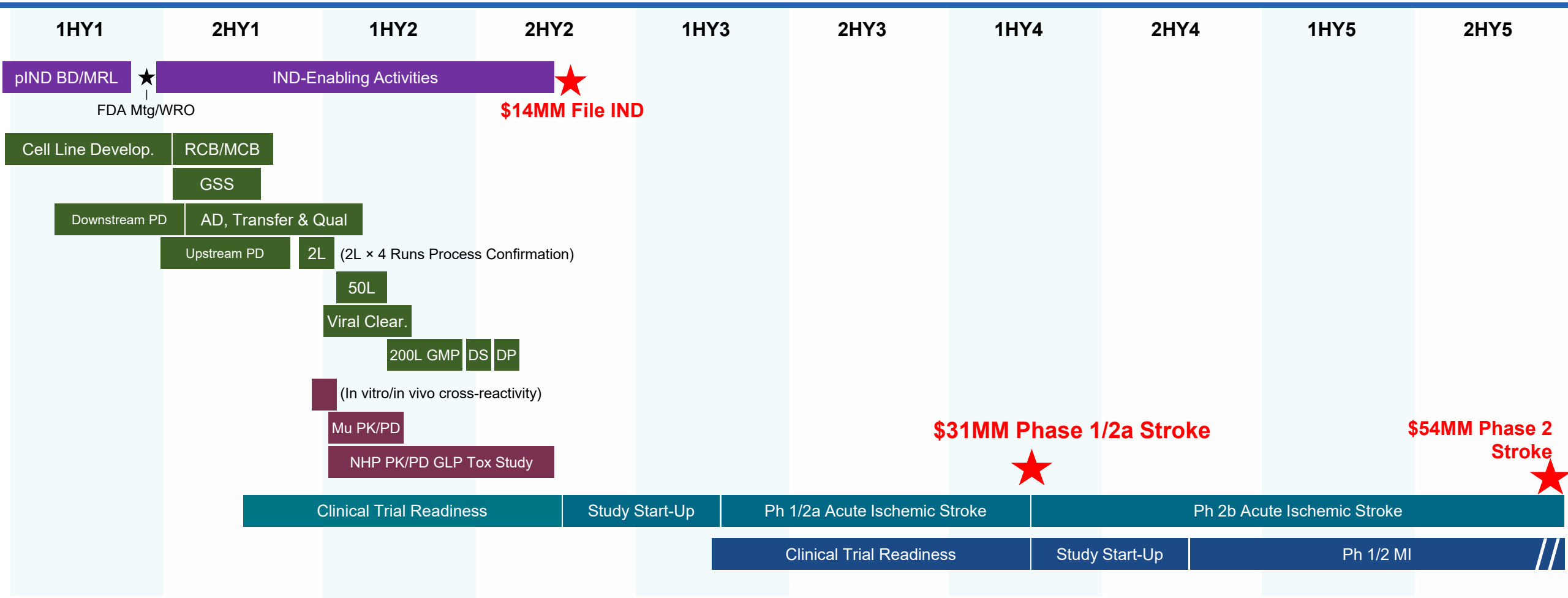


* *Randomization 1:1:1:1 & Stratification: Treatment Window ≤ 9 hr vs >9-24 hr and Baseline Infarct Size*

Safety Endpoints
- Incidence, severity & relationship of AEs
- Mortality and final disposition
- Change from baseline in laboratory analytes

Efficacy Endpoints
- Change in infarct volume from baseline to Days 2 and 5 as assessed by DW-MRI
- Incidence of arrhythmias
- Change in NIHSS, mRS and BI from baseline to Days 2, 5, 30 and 90

5 Year Development Plan - VB-001 (Anti-Sdc2 mAb)



Abbreviations: **AMD**= Age-Related Macular Degeneration; **GSS**=Generational Stability Study; **pIND**=preIND Briefing Document; **MI**=Myocardial Infarction; **MCB**=Master Cell Bank (include. generation and characterization); **MRL**=Meeting Request Letter; **RCB**=Research Cell Bank; **SSU**=Study Start-Up; **WRO**=Written Response Only

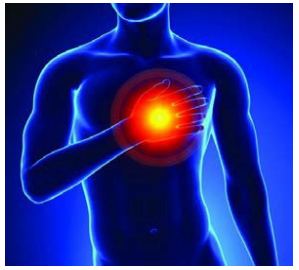
VST-Bio Second Indication: Acute Myocardial Infarction

The leading cause of death and disability worldwide

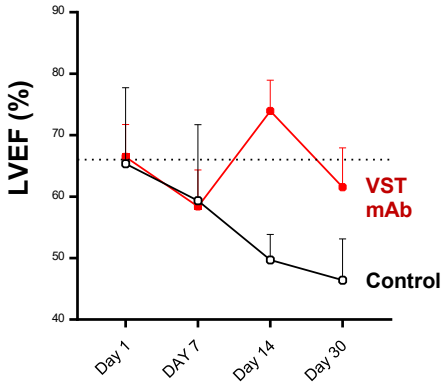
Animal Model (Yale)

Inhibition of vascular leakage/vasogenic edema In mouse infarct model led to:

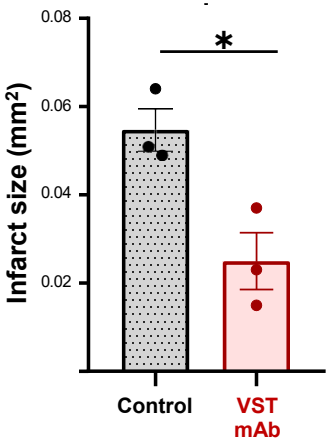
- Reduced infarct size/tissue damage (by 56%)
- Reduction of vascular leakage/permeability
- Improved cardiac function (ejection fraction, FAC, CO)
- Control mice develop *severe heart failure* within 30 days
- VST anti-sdc2 mAb treated mice have complete normal hemodynamics



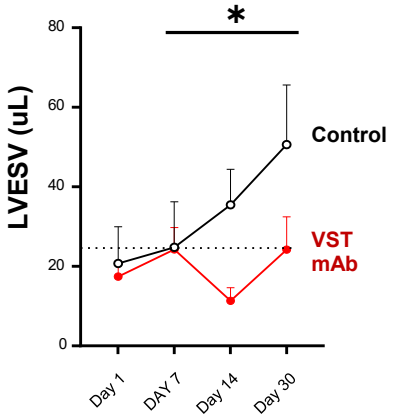
Post-Infarct LV Function



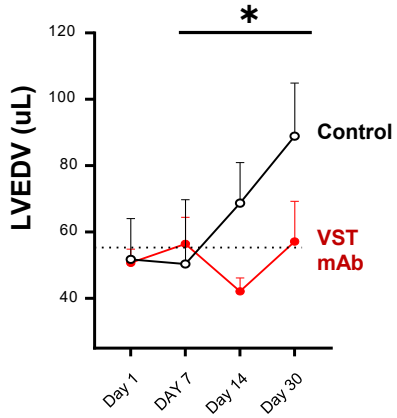
Infarct Size (mm^2)



LV End Systolic volume



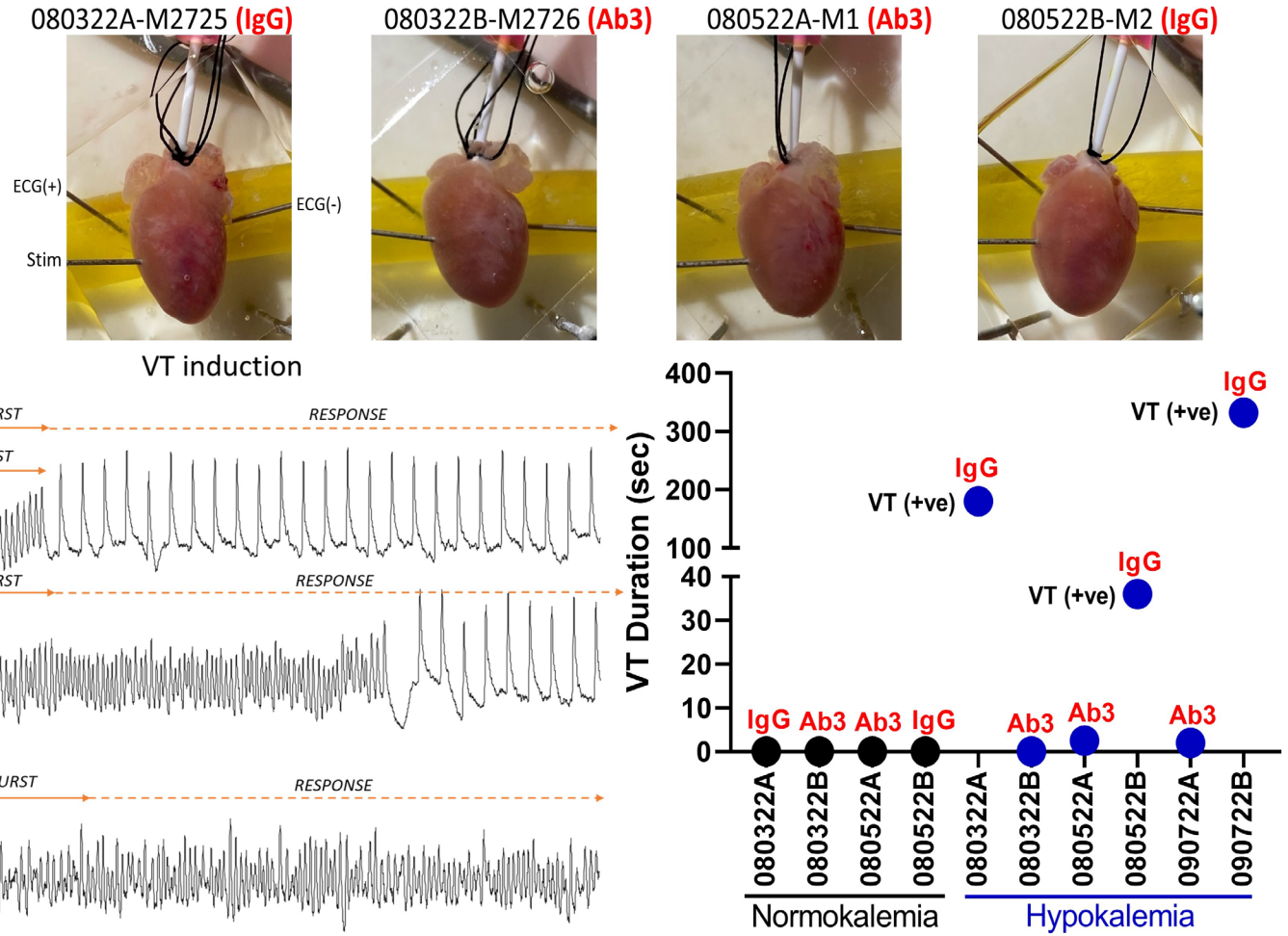
LV End Diastolic volume



Corti & Simons, Yale University (2022)

Sdc-2 Antibody Blocks Arrhythmias

- Cardiac arrhythmias are highly prevalent during the acute phase of stroke (25%) and MI (90%); these harm patients by hemodynamic instability and sudden cardiac death
- *Increase in interstitial fluid* in response to I/R injury may be a key factor in the promotion of post-ischemic arrhythmias
- Treatment of mice with an anti-Sdc2 Ab at the time of I/R injury fully suppressed the incidence ventricular tachycardia



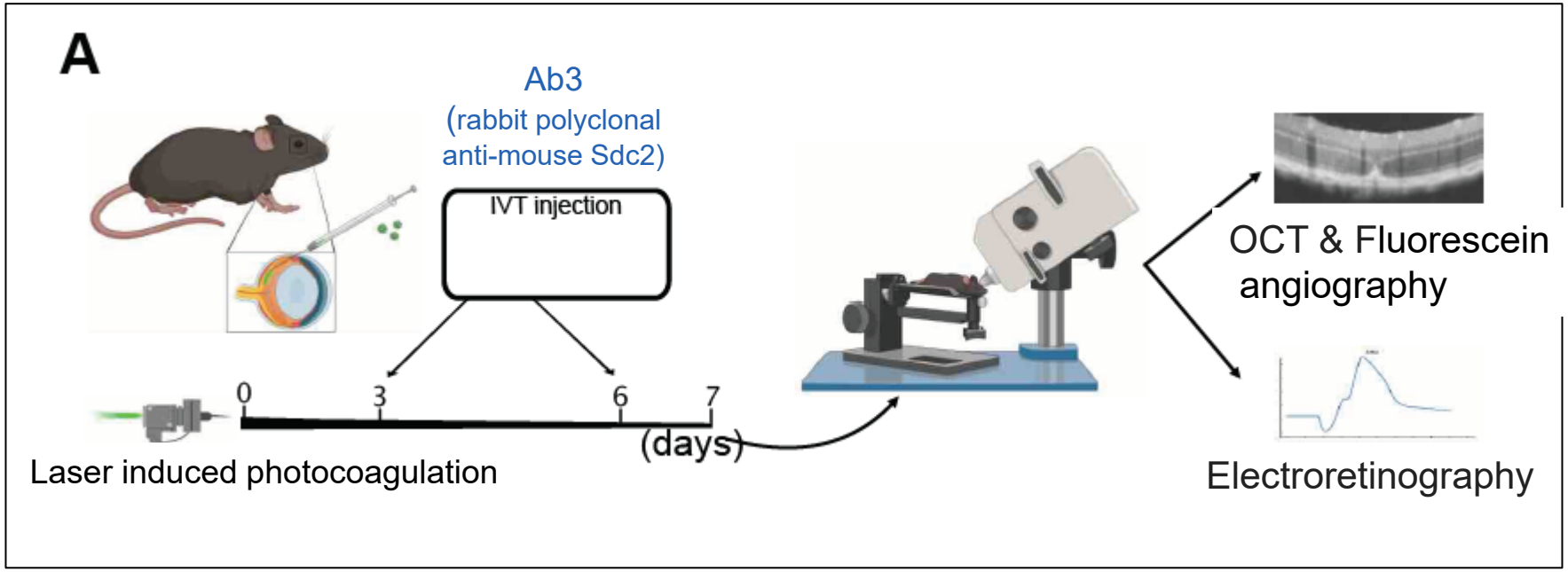
VST-Bio Third Indication: Age-Related Macular Degeneration (AMD)

- Alteration of visual acuity in wet AMD is mostly driven by VEGF-A-induced edema from leaky newly forming blood vessels below the retina layers.
- All therapies aimed at alleviation of this process rely on inhibition of VEGF-A activity
- While effective in preventing vascular leak and edema, this approach also leads to the loss of normal vasculature and multiple related side effects
  - Anti-VEGF: Side effects include vascular rarefaction and geographic atrophy
  - IVT: Side effects include hemorrhage, bacterial infection, intraocular inflammation, intraocular pressure increase
- In a standard mouse model of AMD, treatments with **systemic or IVT** anti-Sdc2 pAb were as effective as IVT anti-VEGF therapy in reducing edema and local inflammation

Intravitreal administration (IVT)

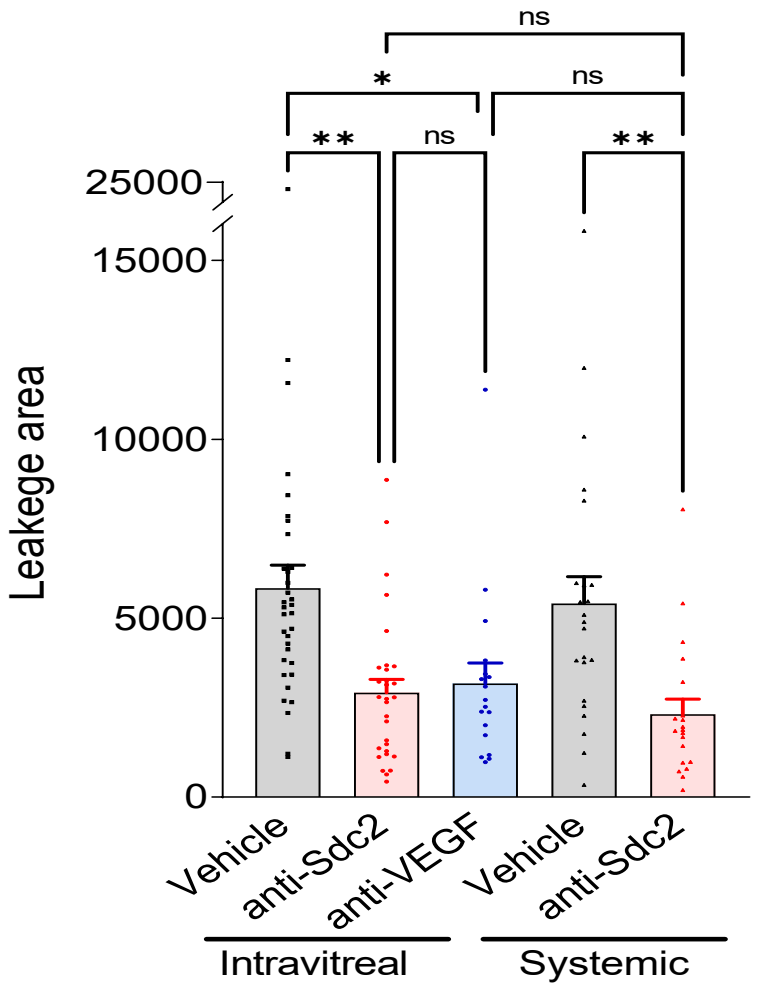
Anti-Mouse Sdc-2 Ab3 Was Tested in the Choroidal Neo-Vascularization Model After IVT and IV Administration

Intravitreal Injection



Tail-vein Injection (systemic)

In vivo Lesion Leakage Area by Fluorescein Angiography (FA)



- Sdc2 Ab, either by systemic or IVT, reduced leakage area by 50%, with no discernible differences between the two different routes
- Similar efficacy as IVT administered anti-VEGF

Both Local and Systemic Anti-Sdc2 Therapy Is Highly Effective and Safe

Multiple Evidence of Safety

Mechanistic studies *in vitro:*

- Sdc2 antibody minimally affect VEGFA-VEGFR2 signaling (only Y951 is reduced; all other critical phosphosites are normal) (Corti et al. Nature Card Research 2022)
- Sdc2 selectively blocks VEGFA-induced permeability and edema (not interference with other critical permeability factors such as TNFα, Thrombin, Histamine
- All beneficial effects of VEGFA in endothelial cells are preserved (e.g., proliferation, migration, cytoprotective and pro-survival effect) (Corti et al. Nature Card Research 2022)

***In vivo*: Mouse:**

- Sdc2 knockout mice develop normally; they are healthy and have long life span (comparable to wild type mice)[1]
- Y949F transgenic mice (that mimic Sdc2 antibody) develop normally, are healthy and have long life span[2]
- Systemic injection of Sdc2 antibody in mice dose not lead to changes in BP or impair wound healing
- Both intravitreal and systemic injections safe

***In vivo*: NHP:**

- No clear signs of organ toxicity up to 10mg/Kg at 7 days post injection (from histochemistry of brain, liver, lung, kidney, spleen, heart)
- No changes in blood chemistry (i.e., complete blood count, liver function panel, kidney function, blood oxygenation, lipid panel, CRP and fibrinogen)
- Confer neuroprotection after stroke

1. Corti et al. Nature Communications 2019
2. Claesson-Welsh lab., Nature Communications 2016, Elife 2020

Intellectual Property

- **Methods and Compositions to Alleviate Vascular Permeability**
- **Methods and Compositions to treat vascular Leak**
- PCT/US2021/033759 (Nov 24 2020)
- No. 63/029,062; PCT/US2019/034644;
- No. 62/678,493; US 2021/0113654 A1

Yale Licensed IP

- **Selective Regulation of Vascular Permeability (Human Antibody Composition Patent)**
- 63/444,520 – 14765-005-888; 63/338,359

- **Selective Regulation of Vascular Permeability for Treating Ischemic Stroke**
- 63/444, 521 – 14765-006-888, Feb 9 2023 – Utility Patent

- **Selective Regulation of Vascular Permeability for Treating Age-related Macular Degeneration**
- 63/495,763; 14765-007-888; 4-12-2023 – Utility Patent

- **Selective Regulation of Vascular Permeability for Treating Acute Myocardial Infarction**
- 63/495,765; 14765-008-888 – Utility Patent

VST BIO IP

VST-Bio Company Summary

- VST-Bio First-in-Class Human Antibodies target a novel pathway regulating vascular permeability/leakage known to be associated with multiple pathologies, resulting in:
  - Reduced vasogenic edema formation, and inflammation in ischemic stroke
  - Therapeutic effect in ischemic stroke (infarct size) can be achieved even when initiated late (<24 hrs.) after onset of stroke, in contrast to conventional standard-of-care therapy that is only effective when initiated within 4 hrs. after disease onset
  - High dose intravenous infusion was well tolerated, safe, and dose-dependently inhibited vascular leakage in small and large animal models, including primate model
- Looking for investment/partnering deals to raise up to $31M to complete a Ph I/II clinical study in stroke ($14M to IND)

VST BIO CORPORATION
Vascular Therapeutics

Thank You

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