Lumen-oriented versus wall-oriented treatment strategies for intracranial aneurysms – a systematic review of suggested therapeutic concepts

Supplementary Materials
Supplementary Figure 1 – Extracranial aneurysm models classified according to Marbacher et al. 2020 (modified from J Cereb Blood Flow. 2020 May;40(5):922-938.)
Supplementary Figure 2 – Creation time for intracranial aneurysm models classified according to Strange et al. 2020 (modified from Brain Sci. 2020 Feb 27;10(3):134.)

W: Common carotid artery (CCA) ligation only
X: CCA Ligation and renal artery (RA) ligation
Y: Elastase only
Z: Elastase and CCA ligation
**Supplementary Table 1**: Lumen-oriented IA treatment approaches. Strategies tested in clinical trials are marked in bold.

| Enhanced intraluminal healing               |                                                                 |
|--------------------------------------------|------------------------------------------------------------------|
| **Coil coating**                            | • Silk (1), clinical trial nylon (2), dacron (3)                 |
|                                            | • Fiber coils; Polyurethanes (4), Gold (5)                       |
|                                            | • ECM (types I and IV collagen (6-9), fibronectin (10), laminin (10), vitronectin (10), and tenasin-C (11)) |
|                                            | • SEK-1005 (drug that promotes wound healing through inducing transforming growth factor b (TGF-b) (12) |
|                                            | • Simvastatin (13)                                               |
|                                            | • Polyglycolide endovascular coils (PGA) (14), bioabsorbable polymeric coils (PGLA) (15, 16) Matrix2 coils (17) clinical trial (18, 19), Cerecyte (20) |
|                                            | • Gellan sulfate core platinum coil with tenasin-C (21, 22)      |
|                                            | • Osteopontin and interleukin-10 (23, 24)                       |
|                                            | • Silk fibroin, consisting of stromal cell-derived factor-1alpha (SDF-1alpha) (25) |
|                                            | • Shape memory polymer foam-coated coils (26)                    |
| **Growth factor stimulation**              | • bFGF (mediated by cells (27), hydrogel (28-30), PVA core (31, 32), microcoil (33) |
|                                            | • TGF-β, coil mediated (34), added to gelatin sponges (35)       |
|                                            | • VEGF, mounted on coils (34, 36, 37) or VEGF coupled to a pH-responsive chitosan polymer (38) |
|                                            | • rhSDF-1alpha (recombinant human stromal cell-derived factor 1alpha) (39, 40) |
| **Tissue allograft transplantation**       | • Fibroblasts, coil mediated (41, 42) and collagen-gel coil mediated (43), gelation or gel polymer (44)) |
|                                            | • Modified fibroblasts (bFGF (27), BMP-13 (45))                 |
|                                            | • Endothelial progenitor cells seeded in fibrin polymer (46)     |
|                                            | • Mesenchymal stem cells (47-50)                                |
|                                            | • In situ beta radiation (51-53), clinical trial (32P-coil) (54) |
|                                            | • Chemokine MCP-1 (55, 56)                                      |

| Enhanced intraluminal packing              |                                                                 |
|--------------------------------------------|------------------------------------------------------------------|
| **Expandable coils**                       | • Hydrogel filaments (57, 58)                                    |
|                                            | • Hydrogel coils (59), clinical trial (60)                       |
|                                            | • Electro-responsive hydrogel (61)                              |
| Complex shaped coils | Complex-coil → clinical trial (62, 63)  
360°-coil → clinical trial (64)  
3D-coil system → clinical trial (65, 66)  
Coil-in-shell (67) |
|---------------------|-----------------------------------------------------------------------------------|
| Liquid embolique agents | Iron acrylic (68)  
Fibrin sealant (69, 70)  
Celluloseacetate polymer (71-73) → clinical trial (74)  
Cyanoacrylate (75-78), alginate (79, 80) and chitosan (38, 81-83)  
Ethylene-vinyl alcohol copolymer (84) → clinical trial (ONYX) (85)  
n-butyl cyanoacrylate, Lipiodol, and ethanol (balloon assisted) (86) / n-butyl cyanoacrylate-lipiodol-Iopamidol (87)  
PHIL 35 (fast precipitating, non-adhesive liquid embolic agent), FRED assisted (88)  
Thermoreversible gelatin polymer (89, 90)  
PPODA-QT (a liquid-to-solid gelling polymer system that is polypropylene glycol) diacrylate and pentaerythritol tetraakis (3-mercaptopropionate) (91, 92)  
Shape memory polymer/polyurethane foam (93)  
Liquid to solid dual-gelling poly(N-isopropylacrylamide)-based polymer systems (94)  
Liquid urethane (95)  
Gel-in-shell (67)  
Chitosan-doxycline hydrogel (96) |
| Bridging the intraluminal space | Cellulose porous beads (97)  
Flow-diverter assisted microsphere embolization (98) |
| Stent systems | Neuroform (99) → clinical trial (100)  
Enterprise (101) → clinical trial (101)  
Leo → clinical trial (99, 102-105)  
Honeycomb microporous covered stent (106) → clinical trial (107)  
Accero (braided stent with porosity) (108) → clinical trial (109) |
| Flow diverter | Pipeline → clinical trial (110, 111)  
Silk → clinical trial (112, 113)  
Surpass → clinical trial (114, 115) |
| 3D-devices/Flow disrupters         | • FRED (Flow Re-direction Endoluminal Device) (116) \(\rightarrow\) clinical trial (117)  
|                                  | • Penumbra Liberty (118) \(\rightarrow\) clinical trial NCT01753388  
|                                  | • Derivo (119) \(\rightarrow\) clinical trial (120)  
|                                  | • FD Stent (121)  
|                                  | • TFN (thin film nitinol) (122, 123)  
|                                  | • FD compaction (124)  
|                                  | • FloWise (125) \(\rightarrow\) clinical trial (126)  
| 3D-devices/Flow disrupters       | • WEB (127, 128) \(\rightarrow\) clinical trial (129)  
|                                  | • eCLIPs (bridges aneurysm neck, allows coil retention, disrupts flow away from the aneurysm, leaves main vessel and side branches unencumbered by intraluminal metal, and serves as platform for endothelial growth across the neck, excluding the aneurysm from the circulation) (130, 131) \(\rightarrow\) clinical trial (132)  
|                                  | • Pulsar Vascular Aneurysm Neck Reconstruction Device (PVANRD) (133) \(\rightarrow\) clinical trial (134) NCT03383666  
|                                  | • Luna AES (self-expanding ovoid braided implant) (135) \(\rightarrow\) clinical trial (136)  
|                                  | • TriSpan (neck bridging device) (137) \(\rightarrow\) clinical trial (138)  
|                                  | • Embolic-containing device (ECD, neck bridging detachable device) (139) \(\rightarrow\) clinical trial (140-142)  
|                                  | • pCONus (stent-like self-expanding nitinol implant) \(\rightarrow\) clinical trial (143, 144)  
| Biodegradable stent             | • Aliphatic polyesters (e.g. poly-lactic acid) (145) \(\rightarrow\) clinical trial (146)  
|                                  | • Magnesium alloy covered stent (147-149)  
| Modified/coated stent and flow diverter | • Phospholipid modified flow diverter (150)  
|                                  | • VEGF loaded Poly(L-lactide-co-caprolactone) Nanofiber Covered Stent-Graft (151)  
|                                  | • Condroitin sulfate and EGF bioactive-coated stent (152)  
|                                  | • Stent releasing basic fibroblast growth factor and argatroban (153)  
|                                  | • Rosuvastatin- and heparin-loaded poly (L-lactide- co-caprolactone) nanofiber stent (154)  
|                                  | • Electrospun fiber-covered stent with programmable dual drug release (155)  
|                                  | • Stents with antithrombogenic hydrophilic polymer coating (156) |
### Combined procedures
- Comaneci neck bridging device (157) → **clinical trial (158)**
- Flow diversion combined with jailed branch occlusion using coils and/or Onyx (159)

### Alternative concepts

**Endothelial denudation**
- Mechanical (160, 161)
- Radiofrequency ablation (162)
- Intra-arterial magnetic microparticles navigated by external magnetic field (163)
- Focused ultrasound (FUS) (164)
- Gamma knife radiosurgery (165)
Supplementary Table 2. Wall-oriented IA treatment modalities. Strategies tested in clinical trials appear in bold.

| Exogenous stimulation of proliferative response |
|------------------------------------------------|
| - Blood coagulation factor XIII (166) |
| - Intravenous factor VIII (166-168) |
| - Basic fibroblast growth factor (169) |
| - AMD3100 (promotion of EPCs into the peripheral blood) (170) |
| - Osteoprotegerin (promoting collagen biosynthesis and vascular smooth muscle cell proliferation) (171) |
| - Angiopoietin-1 (Ang-1) (enhances tube formation, migration, and proliferation ability of endothelial progenitor cells) (172) |
| - MiR-17-5p (promotes re-endothelialization via endothelial progenitor cells) (173) |
| - miR-31a-5p agomir (stimulation of endothelial progenitor cells) (174) |
| - Nrf-2 activation (modulating vascular smooth muscle cell phenotype and function) (175) |
| - Gene therapy (delivery of transgenes to modify cells in the arterial wall) (176) |
| - SRPK1 gene silencing (promotes vascular smooth muscle cell proliferation and vascular remodeling via inhibition of the PI3K/Akt signaling pathway) (177) |

| Prevention of EC and SMC injury |
|---------------------------------|
| - Aminoguanidine (NOS inhibition) (178) iNOS -/- (prevents apoptosis in SMC) (179) |
| - Batroxobin (defibrinogenic agent) (178) reduces wall shear stress by reduction of blood viscosity |
| - Estrogen (beneficial effect on EC function and growth) (180-182) **clinical trial NCT01895881 (withdrawn)** |
| - Bazedoxifene (estrogen receptor modulator) (183) |
| - IL-1β -/- (prevents apoptosis in SMC probably by non-activation of iNOS) (184) |
| - Endothelin B receptor blockage (e.g. K-8794) reduced SMC apoptosis (185) |
| - Fasudil (rho-kinase inhibitor; suppress inflammation, and reduces endothelial dysfunction) (186) |
| - EPO (increased EPC count which maintains endothelial integrity) (187, 188) |
| - ARB, valsartan (189), olmesartan (190)) |
| - Statins (193) **clinical series (191, 192)** (simvastatin (194, 195), pravastatin (190, 195), rosuvastatin (196) atorvastatin (197)) **clinical trial NCT04149483 II (198)** |
Metformin (regulating vascular smooth muscle cell phenotype switching via the AMPK/ACC pathway) (199)

Sitagliptin (stimulates endothelial progenitor cells to induce endothelialization) (200)

ASP4058 (sphingosine-1-phosphate receptor type 1 agonist, promoting endothelial integrity and blocking macrophage transmigration) (201)

miR-133a-3p (restrains endothelial cell damage via suppressing the gsk3β/β-catenin pathway) (202)

**Inhibition of inflammation and oxidative stress**

Vitamin C (203) NF-κβ decoy oligodeoxynucleotide (inhibits transcriptional activity of NF-κβ) (204-206)

Nifedipine (inhibits DNA binding of NF-κβ) (207)

Pitavastatin (inhibits NF-kappaB pathway) (208)

Prostaglandin E receptor antagonist (suppresses NF-κβ-mediated chronic inflammation) (209, 210)

Ets-1 decoy oligodeoxynucleotides (reduces MCP-1 expression in SMC) (206, 211)

Anti-MCP-1 gene therapy (decreases monocytes/macrophage recruitment) (212)

Ibudilast, (predominantly blocks phosphodiesterase-4) decreases macrophage migration (213)

Clodronate liposomes (depletion of monocytes) (214, 215)

Tranilast, emedastine difumarate (inhibits mast cell degranulation, reduces chronic inflammation) (216)

Aspirin (inhibits several inflammatory mediators) (217-221) → Clinical Trial (217)

Doxycycline and minocycline (tetracycline derivates, anti-inflammatory effects) (222)

TNF-α inhibition (prevents induction of proinflammatory/matrix remodeling genes) (223)

TNF receptor (TNFR1)-depletion (suppress inflammatory IA wall responses) (224)

Edaravone, a free radical scavenger (reduces production of ROS) (225)

Eplerenone, mineralocorticoid receptor blocker (inhibits oxidative stress) (226, 227) → Clinical Trial (228)

Apocynine (NADPH oxidase inhibitor) (227)

Pioglitazone (PPARγ agonist) (229, 230)

Angiotensin-(1-7) (231)

Mesenchymal Stem Cell-Derived Microvesicles (Suppression of Mast Cell Activation) (232)

Nr1h2 (liver X receptor β) (glucose-sensing nuclear receptor inhibiting macrophage activation) (233)

Curcumin (inhibition ROS and apoptosis) (234)
- Anagliptin (Sipeptidyl Peptidase-4 inhibitor, suppression of macrophage infiltration/activation) (235)
- Inhibitors of tPA (neuroserpin and PAI-1) or indirect inhibitors (eg, tranexamic acid via inhibition of plasmin) (236)
- Vagus nerve stimulation (237)
- Eicosapentaenoic acid (reduces degenerative changes in the media and macrophage infiltration) (238)
- Tanshinone IIA (Tan IIA) (inhibiting the NF-κB-mediated inflammatory response) (239)
- Adenomatous polyposis coli (Apc) siRNA (regulating the NF-κB signaling pathway mediated inflammatory response) inhibiting the NF-κB signaling pathway mediated inflammatory response (240)
- β-sitosterol (suppressing TNF-α-mediated mechanism) (241)
- miR-448-3p (regulating klf5 expression) (242)
- Paroxetin (disruption of P2X4 purinoceptor) (243)
- Dimethyl fumarate activation of nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which reduces oxidative stress by inducing the antioxidant response element (244)
- Cilostazol (antiplatelet) (245)

| Inhibition of ECM degradation |
|-------------------------------|
| Imidapril (MMP-9 inhibition) (246) |
| Tolylsam (selective inhibitor for MMP-2, -9, -12) (247) |
| SB-3CT (selective inhibitor of MMP-2 and -9) (222) |
| NC-2300 (selective inhibitor for cysteine cathepsins) (248) |
| PHA 680623, Rapamycin, and Forskolin (stabilization of primary cilia) (249) |
**Supplementary Table 3** – Study details (including species used, experimental model, main results and conclusion) of preclinical concepts to improve the treatment of intracranial aneurysms.

*Models are classified according to Supplementary Figure 1 for extracranial aneurysm models (A1-E8) and Supplementary Figure 2 for intracranial aneurysm models (W-Z).*

| Ref No. | Name               | Year | Species | Model* | Conclusion                                                                                                                                 |
|---------|--------------------|------|---------|--------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 1       | Graves, et al.     | 1990 | Dog     | A1     | Flower petal coils with silk fibers were effective in producing thrombosis of the aneurysms, suggesting that coils of appropriate design may be useful in the endovascular treatment of aneurysms. Other coil designs evaluated, those with simple and complex curves without silk fibers, demonstrated insufficient thrombogenicity and spatial stability. |
| 2       | Ahuja, et al.      | 1993 | Rabbit  | B2     | Authors investigated a modification of the Gugliemi detachable coil (GDC). They developed a rabbit model and coating technique to test differences in thrombogenicity of platinum coils with a variety of polyurethanes. |
| 3       | Whitlow, et al.    | 2009 | Rat     | B2     | Ultrathin coatings of gold provoked a neointimal response and degree of luminal occlusion greater than that of plain platinum aneurysm coils in a rat arterial occlusion model. |
| 4       | Dawson, et al.     | 1995 | Swine   | A1     | Aneurysms treated with collagen microcoils were completely obliterated with a collagen-rich fibrous scar with no histological evidence of residual thrombus or recanalization. After treatment of experimental aneurysms with collagen microcoils, re-endothelialization across the former aneurysm neck was seen. In contrast, aneurysms embolized with dacron-fibered microcoils contained persistent thrombus surrounded by a relatively immature scar with residual aneurysmal lumen and lack of endothelium. |
| 5       | Dawson, et al.     | 1996 | Swine   | A1     | Local fibroblast proliferation and collagen production were stimulated by heterologous cross-linked collagen embedded in micro-coils in this experimental model. Such biologic stimulation holds promise for improving the endovascular cure rate of aneurysms in humans. |
| 6       | Murayama, et al.   | 1997 | Swine   | A1     | Ion implantation combined with protein coating of GDCs improved cellular adhesion and proliferation. Future application of this technology may provide early wound healing at the necks of embolized, wide-necked, cerebral aneurysms. |
| 9 | Tamatani, et al. | 1999 | Dog | B2 | Collagen-coated platinum coils can produce rapid and stable occlusion of embolized vessels. |
|---|---|---|---|---|---|
| 10 | Murayama, et al. | 1999 | Swine | A1 | GDC-Is indicated a more intense inflammatory response in the aneurysm body and dome and faster re-endothelial coverage of the aneurysm neck. This accelerated histologic response may decrease the chances of coil compaction and aneurysm recanalization. This technology may improve anatomic and clinical outcomes in patients harboring intracranial aneurysms. |
| 11 | Toma, et al. | 2005 | Rat | B2 | Placement of TNC-coated coils can remarkably accelerate organization of luminal cavities and reduce their volume, providing improved efficacy of these coils for endovascular embolization. |
| 12 | Sano, et al. | 2010 | Rat | B2 | SCs accelerated intra-aneurysmal organization in our rat aneurysm model suggesting that platinum coils coated with the novel cyclic peptide SEK-1005 may prevent recanalization and improve the clinical outcome in patients treated by coil embolization. |
| 13 | Kodama, et al. | 2013 | Rat | B2 | Organized tissues that formed around the coils coated with simvastatin were characterized by an accumulation of cells positive for alphaSMA and collagen connective matrix. Tissues also were accompanied by marked formation of endothelium at the orifice of the ECA sac. We suggest that coating coils with simvastatin effectively accelerated organization within the aneurysms and endothelialization over the coil. |
| 14 | Abrahams, et al. | 2001 | Rat | B2 | BPCs enhanced the vascular response of CCA segments compared with GDCs, and were also suitable for local protein delivery to the vessel lumen, under conditions of stasis and arterial pressurization of vascular cells. |
| 15 | Murayama, et al. | 2003 | Swine | A1 | Matrix accelerated aneurysm fibrosis and neointima formation without parent artery stenosis. The Matrix system might prevent aneurysmal recanalization after endovascular treatment of cerebral aneurysms. |
| 16 | Murayama, et al. | 2001 | Swine | A1 | BPM/GDCs accelerated aneurysm fibrosis and intensified neck neointima formation without causing parent artery stenosis or thrombosis. Use of BPM/GDCs may improve long-term anatomical outcomes by decreasing aneurysm recanalization due to stronger in situ anchoring of coils by organized fibrous tissue. Retraction of this scar tissue may also decrease the size of aneurysms and clinical manifestations of mass effect observed in large or giant aneurysms. |
|   | Authors            | Year | Species | Score | Summary                                                                                                                                                                                                 |
|---|--------------------|------|---------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|17 | Mitome-Mishima, et al. | 2016 | Swine   | A1    | Aneurysms embolized with Matrix2 coils build thicker scaffolds for endothelialization, but this is not necessarily evidence of earlier tissue proliferation and maturation than those embolized with BP coils. Matrix2 coils may not be superior to BP coils for preventing aneurysmal recanalization after endovascular treatment of cerebral aneurysms. |
|21 | Hamada, et al.      | 2014 | Rat     | B2    | A newly developed coil, GSCC-TNC, may be effective for improving intra-aneurysmal organization after coil embolization.                                                                                     |
|22 | Miura, et al.       | 2016 | Rabbit  | B3    | GSCC-TNCs promote intra-aneurysmal clot organization in simulated clinical settings using Rabbit possibly through the TGF-beta and MMP-9 upregulation.                                                      |
|23 | Chen, et al.        | 2016 | Rat     | B2    | Possible application of OPN and IL-10 coated coils in aneurysm treatment to overcome the recurrence.                                                                                                         |
|24 | Hosaka, et al.      | 2017 | Mouse   | B1    | IL-6 and OPN are key downstream mediators of MCP-1-mediated intra-aneurysmal healing.                                                                                                               |
|25 | Gao, et al.         | 2016 | Rat     | B2    | SDF-1alpha-coated coils with MSC or EPC transplantation may be beneficial in the aneurysm healing and endothelialization at the orifice of embolized aneurysm.                                                 |
|26 | Jessen, et al.      | 2020 | Rabbit  | B1    | When considering cell types and extracellular matrix composition, the overall host response scores were significantly better in FCC-treated aneurysms at the later time point. Based on results of these metrics, the FCC device may lead to an advanced tissue remodeling response over BPC occlusion devices. |
|28 | Hatano, et al.      | 2003 | Rabbit  | A1    | Local, controlled release of sufficient amounts of bFGF with polyethylene terephthalate fiber coils coated with gelatin hydrogel accelerated the organization of aneurysms.                                         |
|29 | Hong, et al.        | 2001 | Rabbit  | A1    | Local controlled release of bFGF stimulated the formation of in vivo fibrosis, resulting in obliteration of the aneurysm. Long-term results of the fibrous organization remain speculative.                                                    |
|30 | Kawakami, et al.    | 2006 | Rabbit  | A1    | Local, controlled release of bFGF from the hollow fibers combined with gelatin hydrogel incorporating bFGF accelerated the aneurysm healing by tissue organization.                                                 |
|31 | Matsumoto, et al.   | 2003 | Rat     | B2    | FGF-core coils may be effective in inducing fibrotic changes inside aneurysms. These coils may be used as an embolic material to cure cerebral aneurysms.                                                       |
|32 | Tsumoto, et al.     | 2007 | Rabbit  | B1    | Implantation of the PVA-core coil containing bFGF accelerated tissue growth at the neck as well as in the dome of aneurysms induced by elastase in Rabbit. These aneurysms.                                             |
| Study                                    | Year | Species | Model | Results/Findings                                                                                                                                 |
|------------------------------------------|------|---------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| de Gast, et al.                          | 2001 | Rabbit  | B1    | TGFbeta-coated platinum coils undergo earlier cellular coverage than standard platinum coils, but differences in coverage between coated and control coils are no longer present at later time points. These data suggest that improvements in intra-aneurysmal cellular proliferation resulting from coil modifications, although significant in the early postembolization phase, may dissipate over time. |
| Agrawal                                  | 2013 | Rat     | B2    | The coated GDC with TGF-beta or VEGF appears beneficial in promoting endothelialization, clot organization, and cellular tissue integration of the coils. |
| Raymond, et al.                          | 2003 | Swine and Dog | B1, C1 | Growth factor delivery can be performed with alginate, but formulation changes and improved endovascular control are necessary before contemplating its use in intracranial aneurysms. |
| Abrahams, et al.                         | 2001 | Rat     | B2    | rhVEGF may be beneficial in promoting endothelialization, clot organization, and tissue integration of the coils. This is the first study to hypothesize that rhVEGF may be useful as a surface modification to GDCs for enhancing their therapeutic effects in the treatment of cerebral aneurysms. |
| Ohyama, et al.                           | 2004 | Rat     | B2    | Platinum microcoils coated with immobilized rhVEGF may be effective for the obliteration of aneurysms.                                                                                           |
| Pan, et al.                              | 2010 | Rat     | B2    | Chitosan with a bioactive agent, such as rhVEGF, showed excellent results in occluding aneurysms in a rat model.                                                                                  |
| Li, et al.                                | 2017 | Rabbit  | B1    | Study reveals an important role of rhSDF-1α in inducing aneurysm occlusion and suggests that it achieves its function through modulating the reendothelialization. |
| Marx, et al.                             | 2001 | Rabbit  | B2    | Fibroblast allografts remain viable and proliferate in the vascular space in a rabbit model. Furthermore, these same fibroblasts, after seeding onto platinum coils in culture, remain protected within the lumen of the coils and retained within the coil lumen even after prolonged exposure to arterial blood flow. Coils can be used to deliver viable fibroblasts directly into experimental aneurysms successfully. These findings indicate that coil-mediated cell implantation is feasible and may be a potential method of increasing the biological activity of embolic coils. |
| Dai, et al.                               | 2007 | Rabbit  | B3    | FBC coils can accelerate early histological healing compared with control coils in the rabbit aneurysm model.                                                                                     |
| Dobashi, et al.                          | 2012 | Rat     | B5    | TGP mixed with both dermal fibroblasts and bFGF induced the most advanced thrombus organization in the experimental aneurysms followed by TGP mixed only.                  |
with dermal fibroblasts. TGP may be useful as a delivery device to deploy fibroblasts and cytokines into aneurysms.

|   |   |   |   |
|---|---|---|---|
| 45 | Dai, et al. | 2008 | Rabbit | B1 |
| 46 | Aronson, et al. | 2012 | Rabbit | B3 |
| 47 | Rouchaud, et al. | 2013 | Rabbit | B1 |
| 48 | Adibi, et al. | 2017 | Rabbit | B3 |
| 49 | Kuwabara, et al. | 2017 | Mouse | Y |
| 50 | Avery, et al. | 2019 | Rabbit | B3 |
| 52 | Levesque, et al. | 2004 | Dog | arteries |
| 53 | Raymond, et al. | 2006 | Dog | B2, C1 |
| 55 | Hoh, et al. | 2011 | Mouse | Z |
| 57 | Killer, et al. | 2009 | Rabbit | B1, D1 |

Ad-BMP-13-coated coils can improve neck coverage and dome fibrosis in the rabbit model, even in the absence of observed differences in angiographic outcome.

This novel technique may address reasons for the limited durability of standard coil embolization and provides further avenues to develop improved devices for the care of patients with aneurysms.

Percutaneous seeding of BMSCs may colonize and heal the arterial wall thus limiting aneurysm expansion.

Proof-of-concept study shows that adjuvant MSC therapy for intracranial aneurysms is feasible and may enhance histological improvement of coiled aneurysms at 4 weeks post-treatment.

Intravenous administration of MSCs after aneurysm formation prevented aneurysmal rupture in mice. Protective effect of MSCs against the development of aneurysm rupture appears to be mediated in part by the stabilization of mast cells by MSCs.

While aneurysm morphometric comparisons revealed no differences, significant cytokine alterations were observed in vitro and in vivo, suggesting both anti-inflammatory and proinflammatory processes occurred in the presence of MSCs. Histological analyses suggested that tunica intima hyperplasia was inhibited in the presence of MSCs.

Radioactive coils can be produced by using the binding properties of a $^{32}\text{P}$-oligodeoxynucleotide to platinum. Use of these coils in an animal model was effective in preventing recanalization. This method could be performed on site to provide coils tailored to each intervention.

beta-Radiation can prevent recanalization after coil occlusion. We could not demonstrate any deleterious effects of radioactivity on nervous structure or on neointima formation. Delayed organization of thrombus provides a rational basis to establish an upper limit for $^{32}\text{P}$.

MCP-1 has a critical role in promoting inflammatory intra-aneurysmal tissue healing in an MIP-1alpha- and MIP-2-dependent pathway.

Embolization of experimental aneurysms with hydrogel filaments resulted in durable angiographic and histologic occlusion from 2 to 26 weeks. With improvements, hydrogel filaments free from metallic coils show promise for endovascular use.
| Page | Authors | Year | Species | Code | Description |
|------|---------|------|---------|------|-------------|
| 58   | Killer, et al. | 2011 | Rabbit | A1, D1 | Loading hydrogel filaments with SPIO in an effort to provide adequate visualisation for use in MR-guided interventions. |
| 59   | Kallmes, et al. | 2002 | Rabbit | B1 | Distinct from previous devices aimed at speeding the organization of thrombus, the new device has been designed to entirely fill the aneurysm cavity, with complete or near-complete exclusion of thrombus. Unlike thrombus, the hydrogel material is stable and unaffected by natural thrombolytic processes and thus may diminish observed rates of aneurysm recanalization. We report the angiographic and histologic findings of the new, hybrid device used to treat experimental aneurysms in Rabbit. |
| 67   | Moftakhar, et al. | 2015 | Swine and Dog | A1 | AIOD tested in this study showed promise in terms of acute and chronic occlusion of aneurysms. Our findings suggest that these devices have the potential to promote robust tissue healing at the aneurysm neck, which may minimize aneurysm recurrence. Although proof of principle has been shown, further work is needed to deliver this device through an endovascular route. |
| 68   | Alksne, et al. | 1977 | Dog | B2 | A new iron-acrylic compound Developed for stereotaxic thrombosis of intracranial aneurysms, this new iron-acrylic compound The compound polymerizes rapidly, does not fragment, and is nontoxic. It has been used in a series of experimental animals and in initial clinical cases with good results. Use of this material simplifies and increases the safety of stereotaxic aneurysm treatment. |
| 69   | Moringlane, et al. | 1987 | Rabbit | A1 | Microscopic examination showed complete resorption of the fibrin clot and formation of dense granulation tissue within the aneurysm, which was covered with a layer of endothelial cells after 2 weeks. Results are only tentative and require further experimental studies. |
| 70   | Moringlane, et al. | 1988 | Rabbit | A1 | Complete resorption of the fibrin sealant was observed. The aneurysm cavity was filled with a dense connective tissue covered by a layer of newly formed endothelial cells. |
| 71   | Mandai, et al. | 1992 | Dog | A1, D1 | It rapidly hardened in the shape of the aneurysms, completely obliterating them but preserving the parent vessels in all cases. No distal migration of the polymer was seen. Good results of this experimental trial led to a clinical study using a cellulose acetate polymer. |
| 72   | Macdonald, et al. | 1998 | Dog | A1, C1 | Complete packing of aneurysms with GDC obliterates the aneurysm, but endothelialization does not always occur within 2 months. There are substantial problems with CAP: it is thrombogenic and carries a higher risk of causing arterial
thrombosis. Even if aneurysm is successfully obliterated initially with CAP, the CAP may disappear, leaving the aneurysm completely untreated.

| Reference | Year | Species | Model | Notes |
|-----------|------|---------|-------|-------|
| Yang, et al. | 2001 | Rat and Dog | A1, B2, D1 | CAP is not an ideal embolic material for intracranial aneurysms. Further tests and improvements are needed before it can be widely used clinically. |
| Debrun, et al. | 1984 | Dog | E5 | The Silastic balloon was found to be much more effective than the latex balloon in preventing spillage of IBCA into the lumen. |
| Kerber, et al. | 1985 | Dog | A1 | Although the results are encouraging, we believe that it would be prudent to broaden the animal experimentation rather than begin human use. Because no experimental aneurysm models are yet physiological, apply our results cautiously to human intracranial aneurysms. |
| Raymond, et al. | 2002 | Dog | A1 | Cyanoacrylate embolization is currently difficult to control. Although has the potential to decrease recurrences after endovascular treatment of aneurysms, a safe method for endovascular delivery has yet to be developed. |
| Suh, et al. | 2003 | Rabbit | A1 | Effective glue embolization into the aneurysmal sac is technically feasible. Microcatheter position within the aneurysm, concentration of glue, and direction of the aneurysmal neck angle all must be considered. With a coil framework, glue injection was more complete, without deformity or spillage of the glue from the aneurysm. |
| Becker, et al. | 2007 | Swine | A1 | Calcium alginate was an effective endovascular occlusion material that filled the aneurysm and provided an effective template for tissue growth across the aneurysm neck after 30 days and up to 90 days. Complete filling of the aneurysm with calcium alginate ensures stability, biocompatibility, and optimal healing for up to 90 days in Swine. in swine model? |
| Chabrot, et al. | 2012 | Rabbit | Auricular artery | Viscosity obtained with chitosan and 3% STS permits better control during injection and longer vascular occlusion. These findings, combined with the intravascular neovascularization observed with CH0, led to preferred combination with STS. |
| Fatimi, et al. | 2012 | Dog | E5/E6 | Chitosan/STS hydrogels have great potential as embolizing and sclerosing agents for EVAR and possibly other endovascular therapies. |
| Nakai, et al. | 2004 | Rabbit | A1 | At 30 days, most of aneurysm lumen was replaced with inflammatory cells, and the remaining chitosan was not observed. Severe complications (eg, anaphylaxis) did not occur after the embolization with chitosan. Thus photocrosslinkable chitosan might be a candidate for an embolization material for endovascular treatment of cerebral aneurysms. |
|   | Author, et al. | Year | Animal | Model | Summary |
|---|---------------|------|--------|-------|---------|
| 84 | Raymond, et al. | 2003 | Dog | C1 | HCEVOH embolization of aneurysms without neck protection is feasible. It does not, however, eliminate recurrences in an experimental wide-necked aneurysm model. |
| 86 | Tanaka, et al. | 2015 | Swine | A1 | Although at a preliminary stage, balloon-assisted lipiodol and ethanol injection is feasible for packing a wide-neck aneurysm. |
| 87 | Higashino, et al. | 2020 | Swine | A1 | Configuration of NLI changed at each ratio. NLI231 is a feasible and safe liquid embolic material for balloon-assisted embolization of wide-necked aneurysms in Swine. |
| 88 | Berenstein, et al. | 2016 | Dog | A1, C1 | We developed a new treatment for cerebral aneurysms by combining a retrievable stent and a new liquid embolic agent. |
| 89 | Takao, et al. | 2006 | Swine | A1 | We successfully embolized experimentally produced wide-necked lateral wall aneurysms using TGP, a novel embolic agent. Long-term and pathological evaluations are necessary. By taking advantage of the features of this polymer, such as the capacity to deliver drugs or cultured cells, TGP may also prove useful for the treatment of arteriovenous (AV) malformations, AV fistulas, and tumors. |
| 90 | Takao, et al. | 2009 | Swine | A1 | Experimental aneurysms were safely embolized using TGP. Further modifications related to mechanical stability and long-term safety evaluation results are necessary before clinical application. |
| 91 | Brennecka, et al. | 2013 | Dog | A1 | Study compared neointimal tissue overgrowth in the ostium of experimental aneurysms embolized with PPODA-QT, PPODA-QT plus a framing coil, or coils alone. The coils-only and coil+PPODA-QT groups showed rough and discontinuous ostial surfaces, which hindered neointimal tissue coverage. The PPODA-QT aneurysms consistently produced smooth ostial surfaces that facilitated more complete neointimal tissue coverage over aneurysm necks. |
| 92 | Brennecka, et al. | 2012 | Swine | A1 | This small-scale pilot study highlighted first-time in vivo use of PPODA-QT as an embolic agent for aneurysm treatment. Filling aneurysms to 80% to 90% capacity proved to be a safe and effective delivery strategy, and PPODA-QT showed excellent biocompatibility. This study indicates that Future investigation of PPODA-QT for aneurysm embolization is warranted, as it may prove to be a viable alternative to current embolic materials. |
| 93 | Rodriguez, et al. | 2013 | Swine | A1 | Clotting was initiated within the SMP foam at time 0 (<1 h exposure to blood before euthanization), partial healing was observed at 30 days, and almost complete healing had occurred at 90 days in vivo, with minimal inflammatory response. |
| Page | Author, et al. | Year | Species | CPB | Text |
|------|---------------|------|---------|-----|------|
| 94   | Bearat, et al. | 2013 | Swine   | A1  | With the possibility to engineer hydrogels bottom-up for particular applications, these studies show properties that need to be optimized for dual-gelling polymer systems to serve as liquid-to-solid embolic agents for aneurysm treatment. |
| 96   | Zehtabi, et al. | 2017 | Swine   | Renal artery | An injectable embolizing chitosan hydrogel releasing doxycycline (DOX) was developed as the first multi-faceted approach for occlusion of blood vessels. It combines occlusive properties with DOX sclerosing and MMP inhibition properties, respectively known to prevent recanalization process and to counteract underlying pathophysiology of vessel wall degradation and aneurysm progression. After drug release, the biocompatible scaffold can be invaded by cells and slowly degrade. Local DOX delivery requires lower drug amount and decreases risks of side effects compared to systemic administration. This new gel could be used for prevention or treatment of endoleaks after endovascular aneurysm repair, and the embolization of other blood vessels such as venous or vascular malformations. |
| 97   | Hasegawa, et al.: | 2020 | Rat     | B2  | CPBs may be promising as embolic materials that can induce stable vessel wall regeneration at the neck orifice of an aneurysm without surrounding inflammatory reactions. |
| 99   | Fiorella, et al. | 2004 | Dog     | A1  | Neuroform stent is a useful device for treatment of patients with aneurysms that may not otherwise be amenable to endovascular therapy. In the majority of cases, the stent can be deployed accurately, even within the most tortuous segments of the cerebral vasculature. Although delivery and deployment may be technically challenging, clinically significant complications are uncommon. |
| 106  | Nakayama, et al. | 2016 | Dog, Rabbit | A1 | Excellent embolization performance of the honeycomb microporous covered stents without disturbing branching flow was confirmed at the aneurysms in this proof-of-concept study. |
| 108  | Mühl-Benninghaus, et al. | 2019 | Rabbit Subclavian artery | A1 | Study showed flow remodelling properties of the device prototype with progredient aneurysm occlusion. A larger in vivo study with induced aneurysm should be done to confirm these results. |
| 116  | Ding, et al. 2015 | 2015 | Rabbit | A1 | The Flow-Redirection Endoluminal Device in experimental aneurysms demonstrated high rates of progressive and complete aneurysm occlusion while preserving the patency of branch vessels. |
| 118  | Chavan, et al. | 2015 | Rabbit | B1 | Animal study demonstrated promising results with the novel Liberty stent system. The Liberty showed consistent precise positioning and accurate deployment. Stent revealed good compatibility with embolic coiling procedures, while morbidity and... |
mortality were negligible. In addition, persistent occlusion of aneurysms without recanalization or in-stent stenosis was observed at the 180 day follow-up.

|   | Author(s)            | Year | Model | Device/Technique                                                                 |
|---|----------------------|------|-------|----------------------------------------------------------------------------------|
| 119| Ley, et al.          | 2015 | Rabbit B1 | Derivo Embolization Device provides excellent occlusion of elastase-induced aneurysms while preserving branch arteries. |
| 121| Ma, et al.           | 2015 | Rabbit B3 | New device exhibits high radial stiffness compared to interwoven FD stents and superior longitudinal flexibility. Results from on-going in-vivo experiments and CFD simulations also demonstrated the efficacy of the new device as a FD stent. |
| 122| Ding, et al.         | 2016 | Rabbit B1 | In this rabbit model, the thin film nitinol flow diverter achieved high rates of aneurysm occlusion and promoted tissue in-growth and aneurysm neck healing, even early after implantation. |
| 123| Chen, et al.         | 2016 | Swine A2 | The TFN can be conformally deployed in the curved blood vessel of a swine model without any significant complications or abnormalities. |
| 124| Gentric, et al.      | 2016 | Dog A1 | Compaction of FDs can improve angiographic occlusion of experimental wide-necked aneurysms. |
| 125| Kim, et al.          | 2016 | Rabbit B1 | Newly developed, partially retrievable flow-diverter seems to be a safe and effective tool of aneurysm occlusion, as evaluated in the rabbit aneurysm model. |
| 127| Ding, et al.         | 2011 | Rabbit B1 | WEB device in experimental aneurysms demonstrated promising rates of immediate and long-term aneurysm occlusion. |
| 128| Ding, et al.         | 2016 | Rabbit B1 | Histologic evaluation showed progressive thrombus organization within aneurysm lumen from 1 to 12 months. Results indicated that the WEB II device can achieve high rates of aneurysm occlusion over time in experimental aneurysms. |
| 130| Marotta, et al.      | 2008 | Swine A1 | Aneurysm occlusion with a single extrasaccular endovascular device has potential advantages. The authors believe that eCLIPs may prove to be a useful tool in the endovascular treatment of cerebral aneurysms. The system should reduce risks associated with coiling, procedure time, costs, and radiation exposure. Device satisfactorily occluded 8 experimental sidewall aneurysms. Observed healing pattern was similar to that seen after microsurgical clipping. |
| 131| Marotta, et al.      | 2017 | Rabbit D1 | eCLIPs device permits physiological remodeling of the bifurcation. |
| 133| Turk, et al.         | 2013 | Dog C1 | PVANRD is a novel bifurcation stent that facilitates treatment of wide-necked bifurcation aneurysms compared with currently available adjunctive devices. |
| 135| Kwon, et al.         | 2011 | Rabbit B1 | Luna AES achieved high rates of complete angiographic occlusion and showed promising histologic findings in the rabbit aneurysm model. |
| Page | Author(s) | Year | Species | Model | Study Details |
|------|-----------|------|---------|-------|---------------|
| 137  | Turk, et al. | 2001 | Dog | A1, C1 | TriSpan coil in conjunction with standard GDCs can be used safely and effectively for treatment of wide-necked aneurysms in this canine model. Positioning and deployment of the neck bridge in aneurysms having an acute angle with the long axis of their parent artery are difficult or impossible. It is likely that this device, used in conjunction with the standard GDC, will likely allow treatment of some wide-necked aneurysms that are not treatable with the GDC alone. |
| 139  | Berenstein, et al. | 2009 | Dog | A1, C1 | Within the limitations of this experimental study, treatment of large, wide-necked aneurysms with the ECD and LEA may be feasible. Suboptimal technique and ECD geometry can cause leakage of LEA into the parent vessel or incomplete apposition of the ECD/glue to the aneurysm wall. However, the ECD and glue injection technique did achieve complete occlusion in 1 aneurysm that persisted 1 year later. Histopathological findings in this instance are moderately encouraging. Further investigations of an ECD with N-butyl cyanoacrylate or another LEA are warranted. |
| 145  | Wang, et al. | 2013 | Rabbit | B1 | PGA-FD was an effective device for the treatment of aneurysms and was safe for side branches at 3-month follow-up. |
| 147  | Wang, et al. | 2016 | Rabbit | A1 | Magnesium-alloy-covered stents proved to be an effective approach for occlusion of lateral aneurysm in the rabbit CCA; it provides distinct advantages that are comparable to that obtained with the Willis covered stent. |
| 148  | Cui, et al. | 2017 | Rabbit | A1 | MACS is effective for occlusion of lateral aneurysms and is superior to WCS in growth of the stented CCA and endothelialization. Further work is needed to make this device available for human use. |
| 149  | Nevzati, et al. | 2017 | Rat | A2 | Feasibility of standardized stent occlusion of saccular sidewall aneurysms in Rat - with low rates of morbidity and mortality. This stent embolization procedure combines the opportunity to study novel concepts of stent- or flow-diverter based devices as well as molecular aspects of healing. |
| 150  | Marosfoi, et al. | 2017 | Rabbit | B1 | In the rabbit model, phosphorilcholine surface-modified flow diverters are associated with less thrombus formation on the device surface. |
| 151  | Wang, et al. | 2015 | Rabbit | B1 | The heparin and VEGF loaded nanofiber could provide an approach to fabricate covered stent-graft with properties of anticoagulation and induction of rapid endothelialization. |
| 152  | Lequoy, et al. | 2016 | Dog | E5 | The bioactive coating promoted in vitro cell survival, displayed good durability, and was successfully transferred onto a commercial SG. Preliminary in vivo results suggest improved healing around bioactive Stent grafts. |
| 153 | Arai, et al. | 2019 | Rabbit | B1 | Most of the aneurysm cavity is occupied by loose connective tissues in the group treated with drug-coated stents, whereas extensive massive hematomas are observed in the group treated with drug-free stents. Occurrence rate of in-stent thrombus is small in the drug-coated stents. Stent incorporating bFGF and PLGA microspheres containing argatroban is an effective device for cerebral aneurysm treatment. |
| 154 | Liu, et al. | 2018 | Rabbit | B1 | Rosuvastatin- and heparin-loaded PLCL-covered stents show favorable anticoagulation and pro-endothelialization properties in vitro and in vivo in a rabbit aneurysm model. VEGF-A elevation played a crucial role in rosuvastatin-promoted endothelialization. This work provides an additional option for treating cerebral aneurysms with covered stents. |
| 155 | Zhang, et al. | 2019 | Dog | A1 | Study yields new method to improve the biosafety of covered stent insertion for the treatment of intracranial aneurysms. |
| 156 | Martinez Moreno, et al. | 2019 | Dog | C1 | HPC-coated p64 FDSs appeared to be biocompatible, without acute inflammation. |
| 157 | Gupta, et al. | 2016 | Rabbit | B3 | Comaneci device is a new adjuvant treatment for bridging of wide necked aneurysms with the advantage of averting flow arrest during deployment. No evidence of significant endothelial damage during deployment in preclinical studies. |
| 159 | Fahed, et al. | 2017 | Dog | D2 | Treatment failures after flow diversion of bifurcation aneurysms can be caused by persistent flow to the jailed branch. Branch occlusion combined with flow diversion may improve angiographic occlusion scores of a canine bifurcation aneurysm model. |
| 160 | Raymond, et al. | 2004 | Dog | B2, C1 | Endothelial denudation can prevent recanalization after coil embolization. |
| 161 | Darsaut, et al. | 2007 | Dog | C1 | Stenting led to suboptimal results in the presence of an intact endothelial layer. Endothelial denudation can promote aneurysm occlusion when combined with stenting. |
| 162 | Raymond, et al. | 2010 | Dog | Maxillary and vertebral arteries | RF ablation can prevent recanalization after coil occlusion—at least in the arterial model. Modifications of coils, dedicated neurovascular electrodes, and technique optimization remain necessary before considering a clinical application. |
| 163 | Oechtering, et al. | 2011 | Rabbit | B2 | MMPs can be magnetically directed into aneurysms, allowing short-term obliteration. Although the method has yet to show reliable long-term stability, these experiments provide proof of concept, encouraging further investigation of intravascular magnetic compounds. |
| ID | Authors | Year | Species | Study | Summary |
|----|---------|------|---------|-------|---------|
| 164 | Coluccia, et al. | 2014 | Rabbit | D1 | Presented rabbit model proved suitable and capable of being extended to acquire data on the effect of HIFU on aneurysms and larger vessels. Fact that HIFU led to alteration of aneurysm without inducing rupture encourages further investigations. |
| 165 | Meadowcroft, et al. | 2018 | Rabbit | B1 | Data indicate that GKRS targeted to saccular aneurysms is associated with histopathological changes and linear reduction of aneurysm size over time. Results suggest that GKRS may be a viable, minimally invasive treatment option for intracranial aneurysm obliteration. |
| 166 | Kang, et al | 1990 | Rat | W | Proliferative response at the sites of aneurysm development was modified by exogenous Factor XIII. |
| 167 | Hino, et al. | 2001 | Swine | B2 | Administration of factor XIII may contribute to more effective aneurysm obliteration during coil embolisation. |
| 168 | Hino, et al. | 2004 | Swine | B2 | Administration of wound-healing factor XIII would contribute rapid intimal proliferation and may be effective to facilitate complete obliteration of aneurysms after coil embolization. |
| 169 | Futami, et al. | 1995 | Rat | W | Results demonstrate that exogenous basic FGF induces the proliferative response of smooth muscle cells in aneurysmal lesions in Rat. |
| 170 | Li, et al. | 2017 | Rabbit | B1 | Interval use of AMD3100 promotes the formation of neointima in rabbit saccular aneurysm and facilitates endothelialization of the neointima after FD treatment. |
| 171 | Miyata, et al. | 2020 | Rat | X | Osteoprotegerin suppressed the IA progression by a unique mechanism whereby collagen biosynthesis and VSMC proliferation were activated via TGF-β1 without altering proinflammatory gene expression. Osteoprotegerin may represent a novel therapeutic target for IAs. |
| 172 | Lu, et al. | 2018 | Rat | B2 | Overexpression of Ang-1 enhanced the tube formation, migration, and proliferation ability of EPCs. Ang-1 gene-modified EPCs accelerated organization within the aneurysms and occlusion of aneurysm neck. Transplantation of Ang-1-transfected EPCs may be a new method for the treatment of aneurysm. |
| 173 | Tian, et al. | 2020 | Rat | A2 | miR-17-5p overexpression promoted the vascular repair in aneurysm rat model and increased the level of EPCs in the aneurysm tissues and peripheral blood of the Rat. |
| 174 | Yu, et al. | 2019 | Rat | A2 | Collectively, these results indicate that miR-31a-5p is an important regulator of EPC mobilization and endothelialization and may have a positive effect on aneurysm repair. |
| 175 | Shi, et al. | 2019 | Rat | Y | Results suggest that Nrf-2 exerts protective effects against IA development by preventing VSMCs from changing to a synthetic phenotype. |
| 176 | Abrahams, et al. | 2002 | Rat | B2 | Catheter deployment of platinum or biodegradable gene delivery endovascular microcoils represents an interventional device–based gene therapy system that can serve as a suitable platform for either single or multiple gene therapy vectors. |
| 177 | Li, et al | 2019 | Rat | X | siRNA-mediated silencing of SRPK1 gene inhibits VSMC apoptosis, and increases VSMCs proliferation and vascular remodeling in IA via the PI3 K/Akt signaling pathway. Our findings provide a novel intervention target for the molecular treatment of IA. |
| 178 | Fukuda, et al. | 2000 | Rat | X | NO, particularly that derived from iNOS, is a key requirement for the development of cerebral aneurysm. iNOS induction may be caused by an increase in shear stress near the apex. |
| 179 | Sadamasa, et al. | 2003 | Mouse | X | Inducible NOS is not necessary for initiation of cerebral aneurysm. However, results of this study suggest that regulation of iNOS may have therapeutic potential in the prevention of the progression of cerebral aneurysms. |
| 180 | Jamous, et al. | 2005 | Rat | W | The cerebral aneurysm model was highly reproducible in Rat. Bilateral oophorectomy increased the susceptibility of Rat to aneurysm formation, indicating that hormones play a role in the pathogenesis of cerebral aneurysms. |
| 181 | Jamous, et al. | 2005 | Rat | W | Significant protective role of estrogen against the formation and progression of cerebral aneurysms. It appears to be related to the beneficial effects of estrogen on the function and growth of endothelial cells, which play a major role in preserving the integrity of the vascular wall. |
| 182 | Tamura, et al. | 2009 | Rat | X | A therapy targeted at the endothelium and management of hypertension may help to prevent cerebral aneurysms. |
| 183 | Maekawa, et al. | 2017 | Rat | X | Observation that bazedoxifene decreased the incidence of aneurysmal rupture in ovariectomized rats warrants further studies to validate this response in humans. |
| 184 | Moriwaki, et al. | 2016 | Mouse | X | IL-1beta is important for the progression of cerebral aneurysms in a mouse model. Disruption of the IL-1beta gene results in reduced incidence of mature experimental cerebral aneurysms. |
| 185 | Sadamasa, et al. | 2007 | Rat | X | Results suggest that ETBR might play a significant role in the progression of cerebral aneurysms and have the potential to improve prevention and treatment of cerebral aneurysms. |
| 186 | Eldawoody, et al. | 2010 | Rat | X | Fasudil attenuated induction of cerebral aneurysms in the rat model. |
| 187 | Xu, et al. | 2011 | Rat | X | EPCs may serve as a marker for CA progression and EPO a promising candidate for the clinical management of CA. |
| Citation | Authors | Year | Species | Model | Summary |
|----------|---------|------|---------|-------|---------|
| Liu, et al. | 2016 | Rat | A2 | | EPO enhanced the endothelialization of a coiled embolization aneurysm neck by stimulating EPCs via VEGF modulation. Thus, promotion of endothelialization with EPO provides an additional therapeutic option to prevent recurrence of aneurysms. |
| Aoki, et al. | 2009 | Rat | X | | RAS might play a less important role in CA formation compared to aortic aneurysms or other vascular diseases. This suggests that there are different mechanisms between the pathogenesis of cerebral and aortic aneurysms. |
| Kimura, et al. | 2010 | Rat | X | | Pravastatin reduced both stages III and II+III and olmesartan ameliorated stage III, implying that these may prevent aneurysmal formation by acting on different steps. |
| Brinjikji, et al. | 2017 | Rabbit | B1 | | Systemic statin administration after platinum coil embolization of unruptured aneurysms in a rabbit model does not improve aneurysm occlusion rates at 4 weeks. |
| Aoki, et al. | 2008 | Rat | X | | Treatment with simvastatin suppresses the development of CAs by inhibiting inflammatory reactions in aneurysmal walls. Simvastatin also has a preventive effect on the progression of preexisting CAs and is a promising candidate of a novel medical treatment to prevent CA progression. |
| Tada, et al. | 2011 | Rat | X | | Our results provide the first evidence that cerebral aneurysm growth is partly associated with apoptosis and issue a warning that statins exert bidirectional effects on cerebral aneurysms. Additional intensive research is necessary to understand better their mechanisms and to identify in which patients the administration of statins may elicit deleterious effects. |
| Liu, et al. | 2016 | Rat | A2 | | Rosuvastatin promoted endothelialization of the coiled aneurysm neck via induction of EPCs, suggesting that promoting endothelialization gives an additional therapeutic opportunity during vascular endothelium repair. |
| Qi, et al. | 2018 | Rat | SAH model (cisterna magna punctation) | | Early treatment with atorvastatin effectively ameliorates EBI after SAH through anti-apoptotic effects and the effects might be associated inhibition of caspase-3 and endoplasmic reticulum (ER) stress related proteins CHOP and GRP78. |
| Li, et al. | 2020 | Rat | Z | | Metformin protects against IA formation and rupture by inhibiting VSMC phenotype switching and proliferation, migration, and apoptosis. Thus, metformin has therapeutic potential for the prevention of IA. |
| Yu, et al. | 2019 | Rat | A2 | | Western blot assays showed that sitagliptin activated the expression of NRF2, which is dependent on the function of CXCR4. Furthermore, sitagliptin promoted progenitor |

SAH: Subarachnoid Hemorrhage
endothelial cell migration, invasion and angiogenesis through the SDF-1/CXCR4/NRF2 signaling pathway. Progenitor endothelial cells expressed SDF-1 and VEGF. The promotion of endothelialization by sitagliptin provides an additional therapeutic option to prevent the recurrence of AN.

| 201 | Yamamoto, et al. | 2017 | Rat | X | A selective S1P1 agonist is a strong drug candidate for IA treatment. It promotes the endothelial cell barrier and suppresses the trans-endothelial migration of macrophages in IA lesions. |
| 202 | Jia, et al. | 2020 | Rat | X | Overexpression of miR-133a-3p or downregulation of PSAT1 represses endothelial cell damage and advances endothelial cell proliferation via inhibiting the GSK3β/β-catenin pathway in IA. MiR-133a-3p might be a potential candidate marker and therapeutic target for IA |
| 203 | Dai, et al. | 2013 | Rabbit | B3 | Vitamin C supplementation after platinum coil embolization did not demonstrate improvement of long term occlusion rates of aneurysms. |
| 204 | Aoki, et al. | 2007 | Rat | X | Our data indicate that NF-kappaB plays a crucial role as a key regulator in the initiation of CA development by inducing some inflammatory genes related to macrophage recruitment and activation. NF-kappaB may represent a therapeutic target of a novel medical treatment for CA. |
| 205 | Aoki, et al. | 2009 | Rat | X | Collagen biosynthesis was significantly inhibited at the transcriptional level and in the posttranscriptional enzymatic modification in CA walls through upregulated expression of IL-1beta and the NF-kappaB pathway. Reduced collagen biosynthesis may contribute to CA progression, and inhibition of this process may lead to the prevention of the progression and rupture of CAs. |
| 206 | Aoki, et al. | 2012 | Rat | X | Results suggest the possibility of a minimally invasive molecular therapy targeting the inhibition of NF-kappaB and ets-1 for IAs in humans. |
| 207 | Aoki, et al. | 2008 | Rat | X | Immunohistochemistry and gelatin zymography showed that the expression and activity of MMP-2 was also reduced by nifedipine. Furthermore, nifedipine significantly prevented the enlargement and degeneration of aneurysmal walls of preexisting CAs. Nifedipine may be useful as a medical drug for patients with CAs. |
| 208 | Aoki, et al. | 2009 | Rat | X | Pitavastatin has a suppressive effect on CA progression through the inhibition of NF-kappaB activation in aneurysmal walls. Moreover, pitavastatin treatment can cause the regression of degenerative changes in preexisting CA walls. Pitavastatin is a promising candidate as a novel preventive agent against subarachnoid hemorrhage. |
| ID | Authors          | Year | Species | Model | Signal Pathway/Target |
|----|------------------|------|---------|-------|-----------------------|
| 209| Aoki, et al.     | 2011 | Rat     | X     | Shear stress activated PGE$_2$-EP$_2$ pathway in ECs and amplified chronic inflammation via NF-κB. We propose EP$_2$ as a therapeutic target in cerebral aneurysm. |
| 210| Aoki, et al.     | 2017 | Rat, Mouse | X | Rats administered an EP2 antagonist had reduced macrophage infiltration and intracranial aneurysm formation and progression. This signaling pathway in macrophages thus facilitates intracranial aneurysm development by amplifying inflammation in intracranial arteries. Results indicate that EP2 antagonists may therefore be a therapeutic alternative to surgery. |
| 211| Aoki, et al.     | 2010 | Rat     | X | Inhibition of DNA-binding activity of Ets-1 may lead to prevention of human CA enlargement and rupture. Results of this study will provide clues for a novel therapeutic strategy for CAs. |
| 212| Aoki, et al.     | 2009 | Rat, Mouse | X | MCP-1 plays a crucial role in CA formation as a major chemoattractant for monocyte/macrophage. MCP-1 expression in CA walls is induced through nuclear factor-kappa B activation. MCP-1 may be a novel therapeutic target of medical treatment preventing CA progression. |
| 213| Yagi, et al.     | 2010 | Rat     | Y | Blocking of PDE4 is associated with reduction of inflammation-related molecules and macrophage migration, thereby reducing the progression of cerebral aneurysms. It may represent a new conservative therapy to treat patients with cerebral aneurysms. |
| 214| Mandelbaum, et al.| 2013 | Rabbit | W | During aneurysm initiation triggered by hemodynamics, SMCs rather than macrophages are responsible for MMP production that is critical for aneurysmal lesion development. These SMCs exhibit proinflammatory behavior. |
| 215| Kanematsu, et al.| 2011 | Mouse   | Y | Data suggest critical roles of macrophages and proper macrophage functions in the formation of intracranial aneurysms in this model. |
| 216| Ishibashi, et al.| 2010 | Rat     | X | Mast cells contribute to the pathogenesis of CA by inducing inflammation and that inhibitors of mast cell degranulation can be therapeutic drugs for CA. |
| 220| Li, et al.       | 2015 | Rat     | X | Evidence suggested that aspirin significantly reduced degeneration of aneurysm walls by inhibiting macrophages-mediated chronic inflammation and mobilizing EPCs. |
| 221| Chalouhi, et al. | 2016 | Mouse   | Y | 15-Hydroxyprostaglandin dehydrogenase activation in females reduces the incidence of rupture and eliminates the sex-differential response to aspirin. |
| 222| Makino, et al.   | 2012 | Mouse   | Y | Our data established the feasibility of using a mouse model of intracranial aneurysm to test pharmacological stabilization of aneurysms. Tetracycline derivatives could be potentially effective in preventing aneurysmal rupture. |
| Reference         | Year | Species | Outcome | Summary |
|-------------------|------|---------|---------|---------|
| Ali, et al.       | 2013 | Rat     | X       | Results demonstrate a novel role for TNF-alpha in promoting a pro-inflammatory/matrix-remodeling phenotype. This has important implications for the mechanisms behind intracranial aneurysm formation. |
| Aoki, et al.      | 2014 | Rat     | X       | In this study, using rodent models of IAs, we clarified the crucial role of TNF-alpha-TNFR1 signaling in the pathogenesis of IAs by inducing inflammatory responses, and propose this signaling as a potential therapeutic target for IA treatment. |
| Aoki, et al.      | 2009 | Mouse   | X       | Cerebral aneurysm (CA) formation was markedly inhibited by p47phox deletion in mice and accompanied by decreased inflammation in aneurysmal walls. Data suggested the active participation of ROS and p47phox in CA formation and the therapeutic potential of an ROS-eliminating agent against CA formation. |
| Tada, et al.      | 2009 | Rat     | X       | We demonstrate that mineralocorticoid receptor activation at least partly contributes to the pathogenesis of cerebral aneurysms. |
| Tada, et al.      | 2010 | Rat     | X       | In rat, the destruction of tight junctions may facilitate macrophage migration and cerebral-aneurysm formation. |
| Hasan, et al.     | 2015 | Mouse   | Y       | Endogenous PPARgamma, specifically smooth muscle PPARgamma, plays an important role in protecting from formation and rupture of experimental cerebral aneurysms in mice. |
| Shimada, et al.   | 2015 | Mouse   | Y       | Activation of macrophage PPARγ protects against the development of aneurysmal rupture. PPARγ in inflammatory cells may be a potential therapeutic target for the prevention of aneurysmal rupture. |
| Shimada, et al.   | 2015 | Mouse   | Y       | Findings indicate that Ang-(1-7) can protect against the development of aneurysmal rupture in an AT2R-dependent manner. |
| Liu, et al.       | 2016 | Mouse   | Y       | Human MSC-derived MVs prevented the rupture of intracranial aneurysm, in part due to their anti-inflammatory effect on mast cells, which was mediated by PGE2 production and EP4 activation. |
| Tanaka, et al.    | 2016 | Mouse   | CaCl₂   | Hyperglycemia suppresses macrophage activation and aneurysmal degeneration through the activation of Nr1h2. Although further validation of the underlying pathway is necessary, targeting Nr1h2 is a potential therapeutic approach. |
| Bo, et al.        | 2017 | Mouse   | CaCl₂   | All these data taken together may suggest that curcumin could significantly reduce the CaCl₂-induced cerebral aneurysm through the inhibition of cell apoptosis in the cells. |
| Ikedo, et al.     | 2017 | Rat     | X       | A DPP-4 inhibitor, anagliptin, prevents the growth of IAs via its anti-inflammatory effects on macrophages. |
| ID  | Authors             | Year | Species | Gender | Summary                                                                                                                                                                                                 |
|-----|---------------------|------|---------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 236 | Labeyrie, et al.     | 2017 | Mouse   | Y      | Overall, this preclinical study demonstrates that the tPA present in the blood stream is a key player of the formation of IAs. Thus, tPA should be considered as a possible new target for the prevention of IAs formation and rupture. |
| 237 | Suzuki, et al.       | 2019 | Mouse   | Y      | VNS can reduce aneurysm rupture rates and improve the outcome from ruptured aneurysms.                                                                                                                     |
| 238 | Abekura, et al.      | 2020 | Rat     | W      | Results suggest the potential of the medical therapy targeting GPR120 or using EPA to prevent the progression of IAs.                                                                                       |
| 239 | Ma, et al.           | 2019 | Rat     | X      | Tan IIA can suppress CA formation by inhibiting inflammatory responses in macrophages.                                                                                                                     |
| 240 | Lai, et al.          | 2019 | Rat     | X      | Apc has the potential role to attenuate IA formation and rupture by inhibiting inflammatory response through repressing the activation of the NF-κB signaling pathway.                                       |
| 241 | Yang, et al.         | 2019 | Rat     | Z      | Treatment with β-sitosterol suppresses the development of CA by inhibiting inflammatory reactions including TNF-α and thus β-sitosterol can be a suggestive candidate for the prevention of CA treatment and progression.       |
| 242 | Zhang, et al.        | 2018 | Rat     | X      | The expression levels of KLF5, MMP2, and MMP9 levels were elevated by LPS, and were attenuated by miR-448-3p. These data suggest that miR-448-3p plays the inhibitory role in IA progression, indicating that miR-448-3p overexpression is crucial for preventing the development of IA through downregulation of macrophage-mediated inflammation. |
| 243 | Fukuda, et al.       | 2019 | Mouse and Rat | X | P2X4 is required for the inflammation that contributes to both cerebral aneurysm formation and growth. Enhanced shear stress-associated hemodynamic stress on the vascular endothelium may trigger cerebral aneurysm development. Paroxetine may have potential for the clinical treatment of cerebral aneurysms, given that this agent exhibits efficacy as a clinical antidepressant. |
| 244 | Pascale, et al.      | 2020 | Mouse   | Y      | Dimethyl fumarate demonstrated a neuroprotective effect in mice with a resultant inhibition of oxidative stress, inflammation, and fibrosis in the cerebrovasculature. This suggests a potential role for DMF as a rescue therapy for patients at risk for formation and rupture of IAs. |
| 245 | Suzuki, et al.       | 2018 | Mouse   | Y      | Aspirin prevented aneurysm rupture in a mouse intracranial aneurysm model, while cilostazol did not. Aspirin, the most frequently used drug for patients with ischemic myocardial and cerebral diseases, is also effective in preventing cerebral aneurysmal rupture. |
| #   | Authors         | Year | Species | Result | Study Description |
|-----|-----------------|------|---------|--------|-------------------|
| 246 | Ishibashi, et al. | 2012 | Rat     | X      | Angiotensin-converting enzyme is not involved in the pathogenesis of CA formation. Imidapril suppresses CA formation in an ACE-independent and MMP-9-dependent manner. |
| 247 | Aoki, et al.     | 2007 | Rat     | X      | Macrophage-derived MMP-2 and -9 may play an important role in the progression of cerebral aneurysms. The findings of this study will shed a new light into the pathogenesis of cerebral aneurysms and highlight the importance of inflammatory response causing the degeneration of extracellular matrix in the process of this disease. |
| 248 | Aoki, et al.     | 2008 | Rat     | X      | Data obtained by using NC-2300 revealed an important role of cysteine cathepsins in the progression of CAs. Our findings strongly suggest that an imbalance between cysteine cathepsins and their inhibitor may cause the excessive breakdown of extracellular matrix in the arterial walls leading to the progression and rupture of CAs. |
| 249 | Liu, et al.      | 2017 | Mouse   | Y      | Study provides an important support for the role of primary cilia in development of intracranial aneurysms. The primary cilia stabilizing chemicals might be useful for preventing intracranial aneurysmal development. |
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