METHODS We compared immunosuppression efficiency and safety of a combination strategy using cyclosporine, methylprednisolone and simulect (cocktail group) with cyclosporine alone (cyclosporine group) in cynomolgus monkeys subject to myocardial infarction (MI) with or without cell transplantation. MI was established in thirteen cynomolgus monkeys with permanent ligation of left anterior-descending coronary artery following by direct intra-myocardial injection of H9-EGFPhuman embryonic stem cell-derived cardiovascular progenitor cells (ESC-CVPCs) or cell solution as non-cell control.

RESULTS The cocktail group significantly improved the engraftment rate of transplanted cells and decreased the number of CD3+,CD4+,CD8+ T lymphocytes in the border zone compared with the cyclosporine group at day 3 after transplantation, while the transplanted cells could not be detected either by GFP immunofluorescence staining or QPCR analysis at 20 weeks. More engraftment rate of transplanted cells was associated with reduced apoptotic cells observed in cocktail group compared with that in the cyclosporine group and MI group, but no difference between the cyclosporine group and MI group. Notably, Immune suppression agents in both group caused hepatic dysfunction during use of immunosuppress agents.

CONCLUSIONS The immunosuppression cocktail sufficiently attenuates immune rejection and improves the engraftment of hESC-CVPCs in nonhuman primates compared with cyclosporine alone but both strategies cause the hepatic injury.

GW28-e0898

GCH1 Attenuates Cardiac Autonomic Nervous Remodeling in Canines with Atrial-tachypacing via Tetrahydrobiopterin Pathway Regulated by microRNA-206

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OBJECTIVES Cardiac autonomic nerve remodeling (ANR) is an important mechanism of atrial fibrillation (AF). Our previous study illustrated that miR-206 over-expression exacerbates ANR and AF inducibility by regulating SOD1 expression. GTP cyclohydrolase I (GTPCH-1), encoded by GCH1, is the rate-limiting enzyme in de novo synthesis of tetrahydrobiopterin (BH4), an essential cofactor for nitric oxide (NO) synthesis. Previous studies reported that increased BH4 and NO content negatively regulated nerve regeneration. Besides, decreased BH4 level is related to atrial structural and electrical remodeling. This study investigated effects of GCH1 on ANR via BH4 pathway, regulated by microRNA-206 (miR-206).

METHODS Whole blood samples from AF patients and the controls were collected. The lenti-miR-206, lenti-anti-miR-206, lenti-GCH1, lenti-anti-GCH1, microRNA inhibitor N.C lentiviruses and the negative control lentiviruses were synthesized. 24 mongrel dogs were allocated into two groups: the control group (control, n = 6) and the atrial-tachypacing group (A-TP, n = 18). The A-TP dogs were subjected to continuous right A-TP (400 beats/min) for 4 weeks and randomly divided into 3 groups: the A-TP group, the A-TP + lenti-miR-206 group and the A-TP + lenti-anti-miR-206 group. Another 24 dogs were randomly divided into four groups: the lenti-miR-206 group, lenti-anti-miR-206 group, GCH1 over-expression group and lenti-anti-GCH1 group. Cells were plated in 24-well dishes and transfected with different lentivirus, including lenti-miR-206, lenti-anti-miR-206, lenti-GCH1, lenti-anti-GCH1, lenti-control and lenti-RNAi-NC. Atrial effective refractory period (AERP) was measured with programmed electric stimulation(PES) and the S1-S2 intervals started at 150ms, followed by decrements of 5 ms (S1: S2 = 8: 1). Anti-protein gene product 9.5 (PGP9.5) antibody were used for immunocytochemical staining. Myocardial BH4 content was measured using a ELISA Kit. NO content was measured using a NOX Detection Kit.

RESULTS Patients' plasma was collected and miR-206 expression was up-regulated in AF patients (n=18) than the controls (n=12). In canines, 4 weeks of atrial tachypacing (A-TP), together with miR-206 over-expression, increased PGP9.5(a nerve marker) level. In contrast, a reduction of PGP9.5 level was observed in the lenti-anti-miR-206 canines ($P < 0.01$). After infection of GCH1 over-expression lentiviruses into right superior fat pad(RSFP) for two weeks, AERP was found increased than that in the control group (105.8±1.537ms vs 99.17±2.007ms, $P < 0.05$). In contrast, AERP of canines infected with lenti-anti-GCH1 were found decreased compared with the control group (93.33±1.667ms vs 99.17±2.007ms, $P < 0.05$). GCH1 was validated to be a direct target of miR-206 by luciferase assays. Meanwhile, miR-206 over-expression inhibited atrial GCH1 expression to ~40% of the controls and further reduced BH4 content to 73.6% of the control canines. Moreover, GCH1 over-expression lentiviruses infection attenuated canines' atrial PGP9.5 level to ~56% of the controls. In myocardial cells, transfection of GCH1 over-expression lentiviruses also decreased PGP9.5 expression to 26% of the control group.

CONCLUSIONS Our results demonstrated that GCH1 over-expression increased AERP and attenuated ANR by increasing atrial BH4 and NO content in canine models of A-TP, indicating that GCH1 may inhibit the initiation of AF through attenuating ANR.

GW28-e0941

Increasing fatty acid utilization improves cardiac function through OPA1-mediated mitochondrial fusion in pressure overload-induced heart failure

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OBJECTIVES Several studies on chronic systolic heart failure (HF) have demonstrated that body mass index is inversely associated with mortality, the so-called obesity paradox, but the mechanisms are not entirely clear. Our aim is to investigate to the role of fatty acids metabolism and its underlying mechanism in development of HF.

METHODS The model of HF was produced by transverse aortic constriction (TAC) in C57 mice (6 weeks old). High fat diet (HFD) or normal diet (ND) was fed for 8 weeks. AAV9 was used for myocardium-specific overexpression of CD36.

RESULTS Treatment with high fat diet (HFD, 45% energy as fat) for 8 weeks improved cardiac function and restored cardiac hypertrophy in TAC mice. Specifically, treatment with high fat diet increased mitochondrial fusion and the ratio of L-OPA1/S-OPA1 which were decreased in TAC mice. CD36 overexpression exerted similar effects as treatment with HFD. Mechanistically, fatty acid utilization increased the expression of Yme1l which regulates the processing of OPA1, resulting in the elevation of the L-OPA1/S-OPA1 ratio and the resultant mitochondrial fusion.

CONCLUSIONS These results suggested that increasing fatty acid metabolism in myocardium improves cardiac function through OPA1-mediated restoration of mitochondrial dynamics in pressure overload-induced HF via upregulation of Yme1l.

GW28-e0963

Ginsenoside Rb1 improves learning and memory function in mice

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OBJECTIVES To testify whether ginsenoside Rb1 could improve cognitive function in mice.

METHODS Female C57BL/6 mice were divided into three groups randomly: control group(4 months, n=12); model group(24 months, n=12) and drug group(24 months, n=12). In drug group, ginsenoside Rb1(20mg.kg^{-1}.d^{-1}) was injected into the mice abdominal cavity for 8 weeks, Control group and model group were peritoneal injection with the same amount of normal sodium. The effect of ginsenoside Rb1 on the learning and memory of C57BL/6J mice was tested by Morris water maze.

RESULTS In the acquisition training session, The latency in model group was significantly longer than that in control group ($p<0.05$). In the probe trail, the shorter paths to explore the target quadrant, as well as less times of crossing the place where the platform previously located in probe test than that of aged controls($p<0.05$). However, after treated with Ginsenoside Rb1, The latency was significantly shorter, the time in target quadrant was significantly longer and the crossing the platform numbers were significantly more.

CONCLUSIONS Ginsenoside Rb1 could improve spatial learning and memory of mice.

GW28-e0966

A study on the mechanism of the NF-κB in Ginsenoside Rb1 against the intrinsic aging of mouse brain

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