

New Targets and Treatments for Preventing Heart Failure

Derek Hausenloy

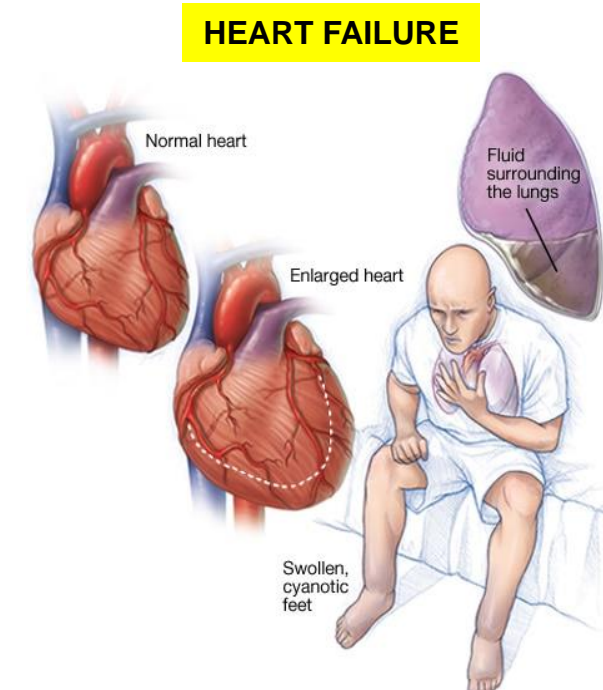
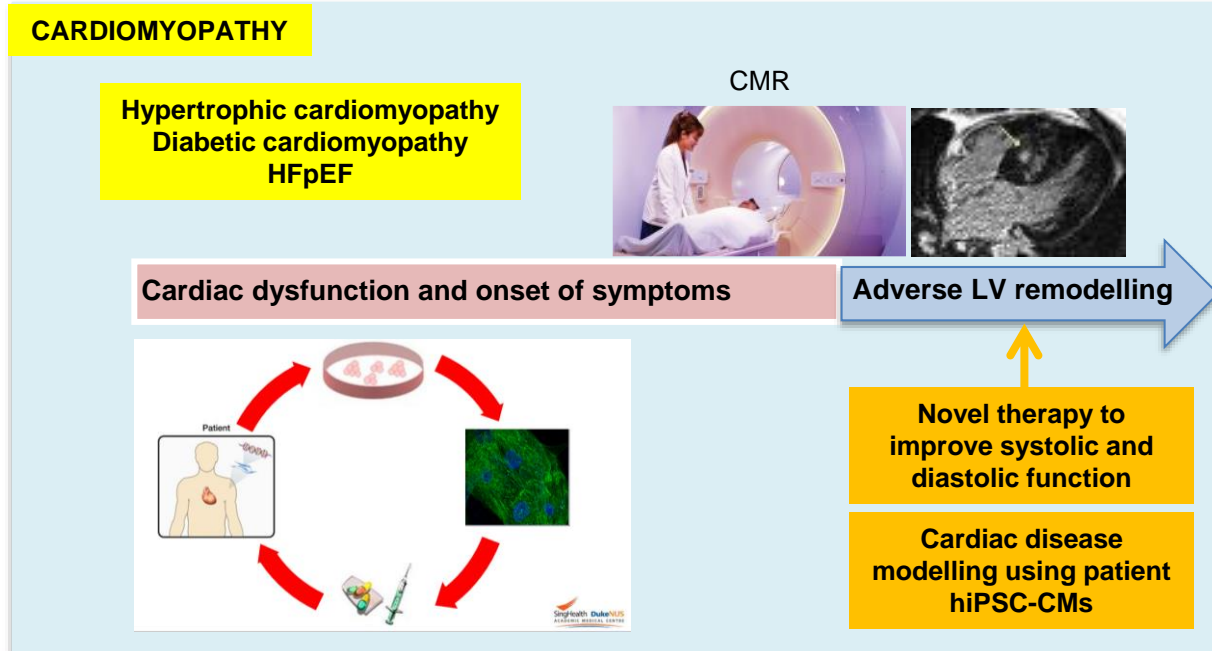
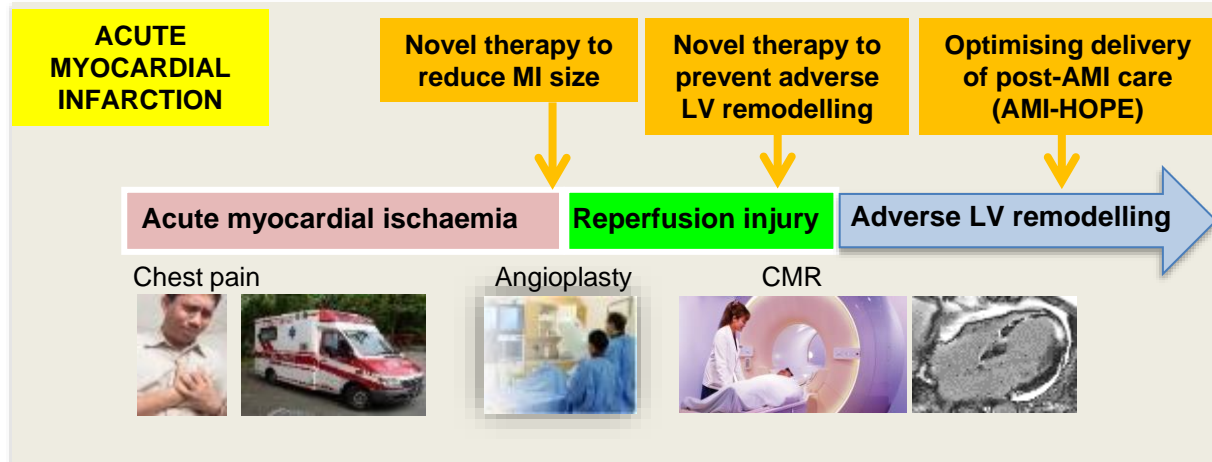
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NMRC AWARDS CEREMONY AND RESEARCH SYMPOSIUM 2021
6 December 2021

Heart Failure

- One of the leading causes of death and disability in SG and worldwide.
- 3rd leading cause of hospitalisation in SG.
- **Multiple aetiologies** - acquired (AMI, DM, HT), familial (HCM).
- Outcomes for AMI patients need to be improved (Death 11% + HF 7% at 12 months – MOH NRDO data).
- *New treatments needed to prevent heart failure and improve health outcomes.*

Cardioprotection – to prevent heart failure



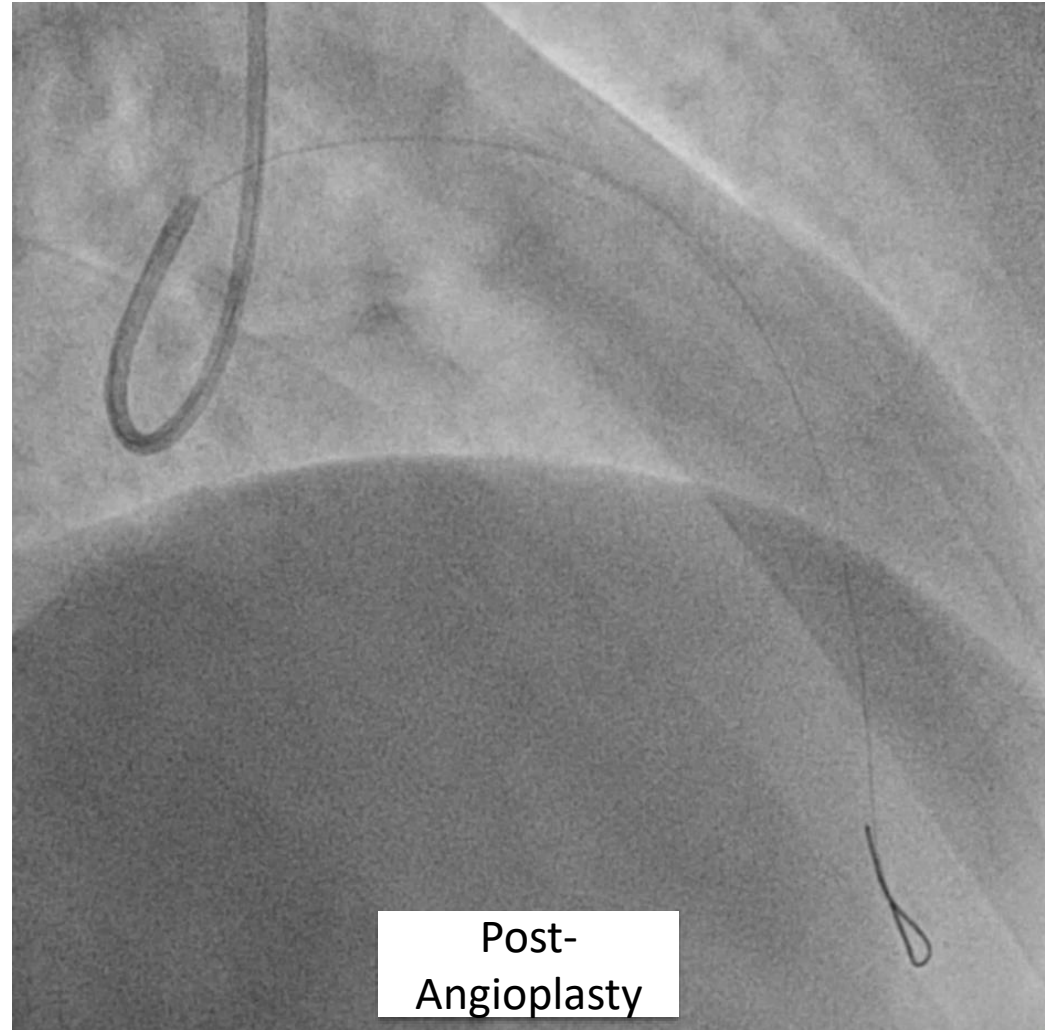
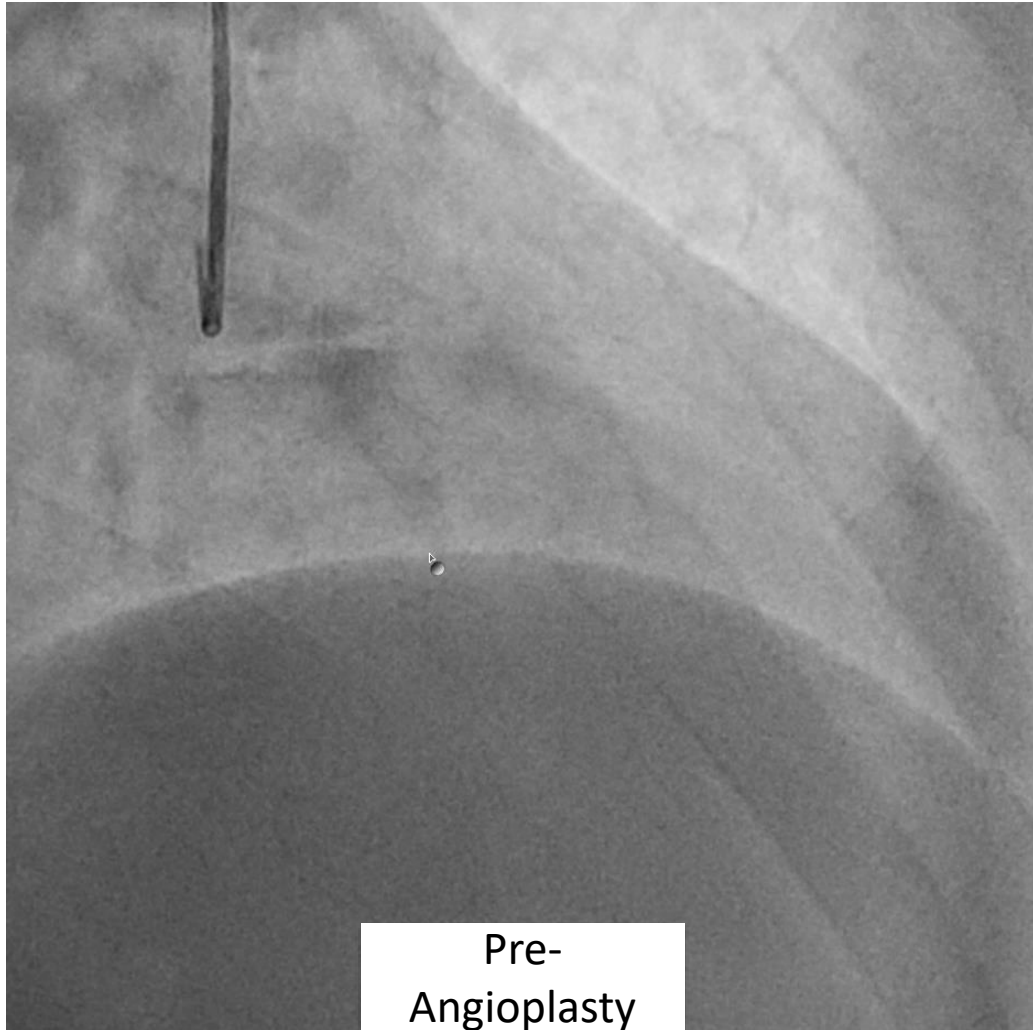
Outline

1. Target mitochondria to reduce infarct size - hydralazine.
2. Platelet inhibition to reduce infarct size and prevent MVO in STEMI (PITRI trial)
3. Improve AMI outcomes using AHP-enabled digital technology (AMI-HOPE study)
4. Use human iPSC-cardiomyocytes to model HCM and identify novel treatment targets – MPO.
5. Target atherosclerosis to reduce PAD complications in DM patients – LOX-1 and IL-11Abs

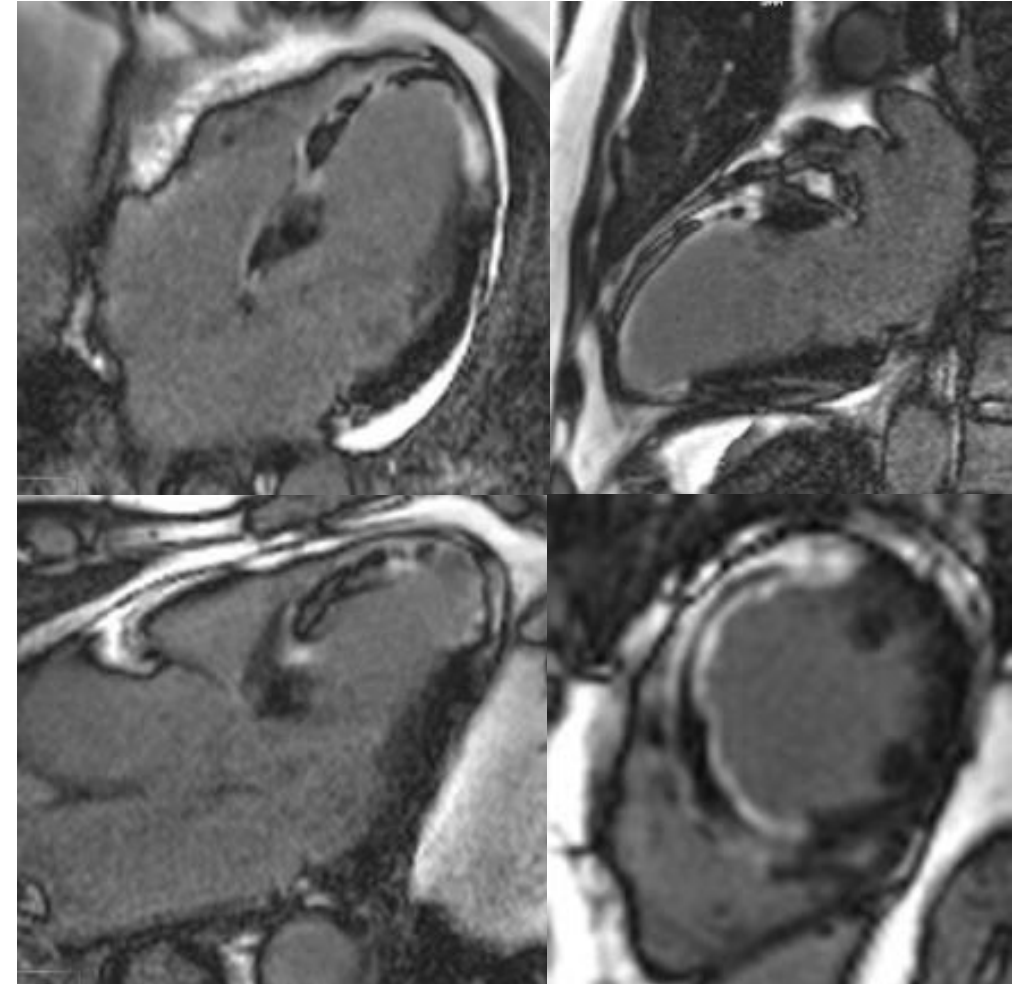
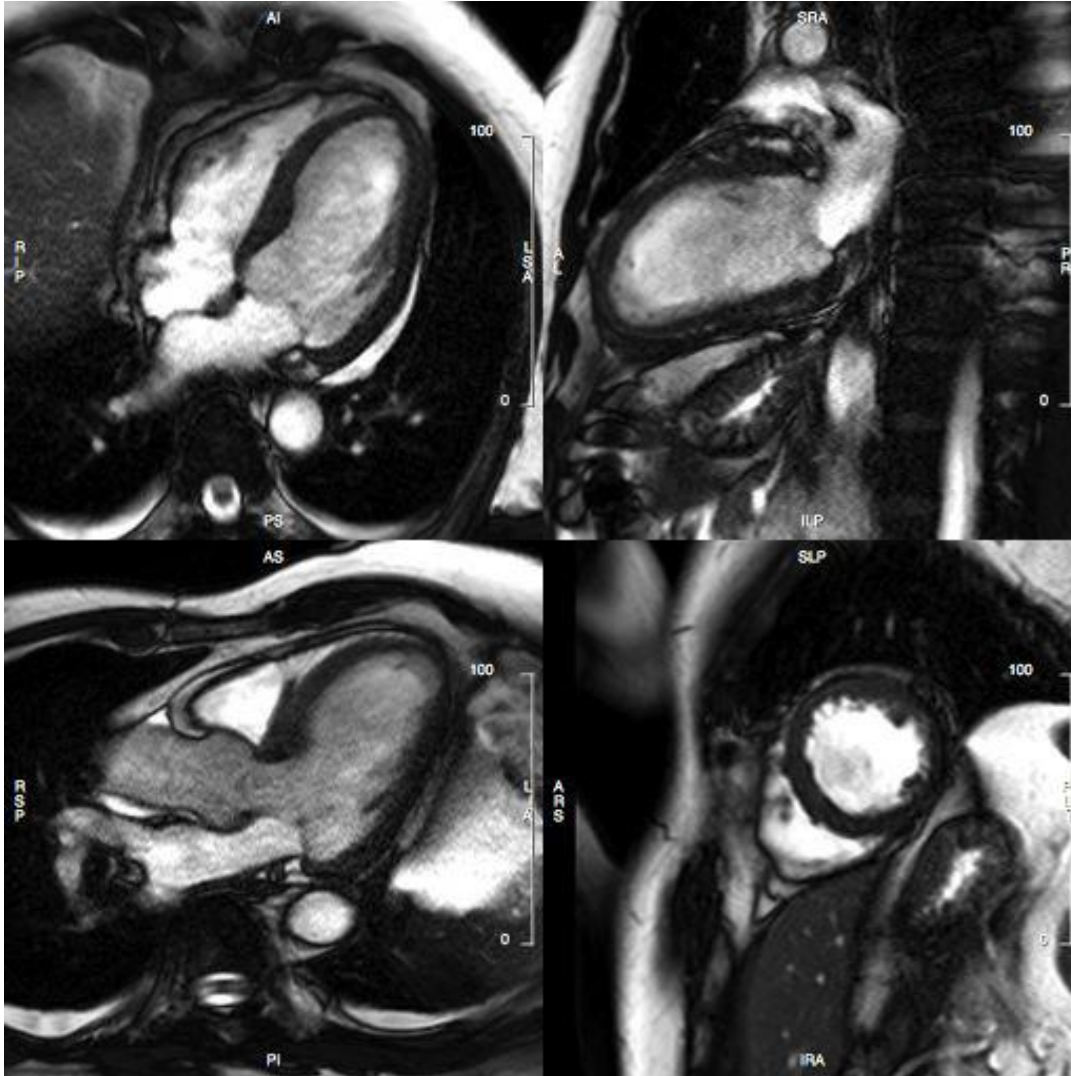
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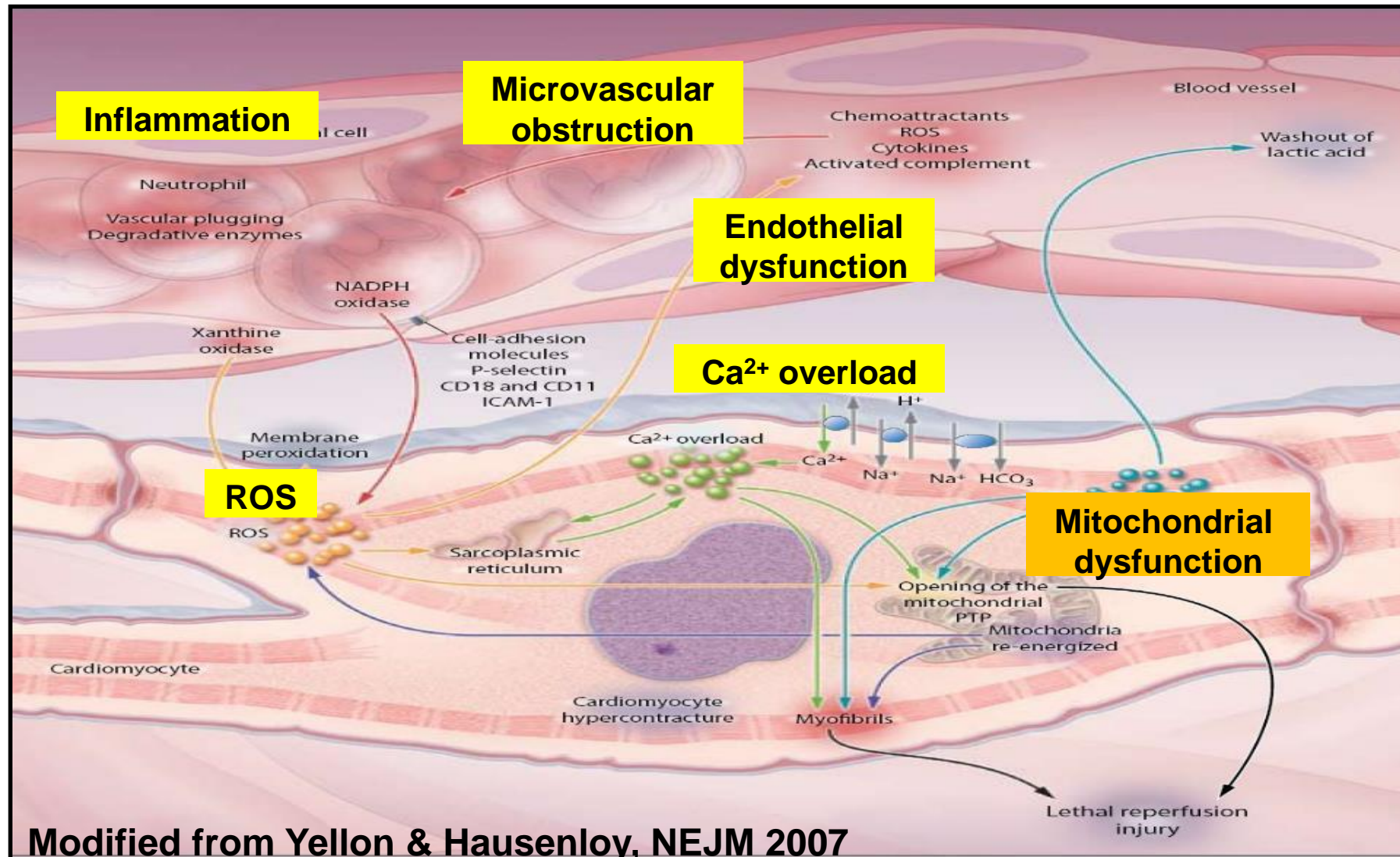
Acute myocardial infarction



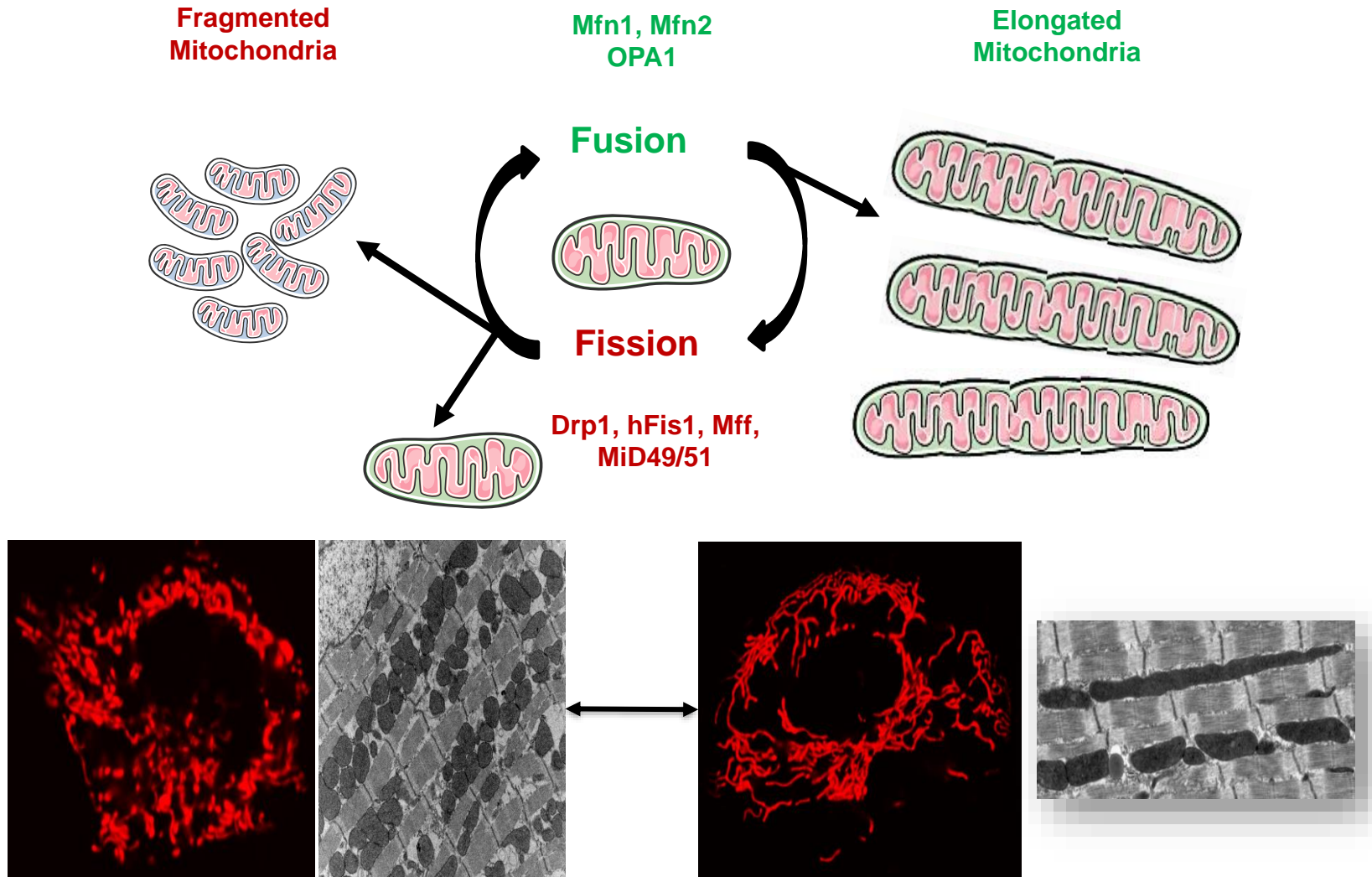
Infarction and impaired heart function despite timely angioplasty



What causes acute myocardial ischemia/reperfusion injury ?



Mitochondria undergo fission in response to acute myocardial IRI

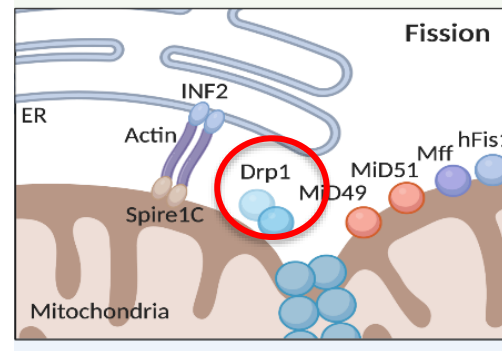


Hydralazine as novel inhibitor of mitochondrial fission

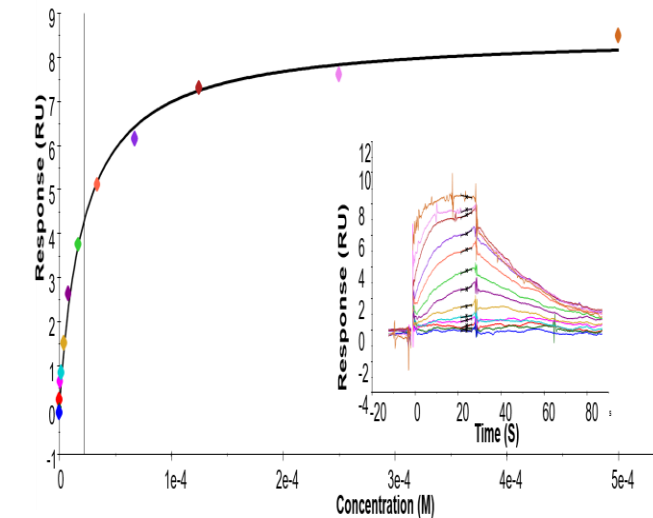
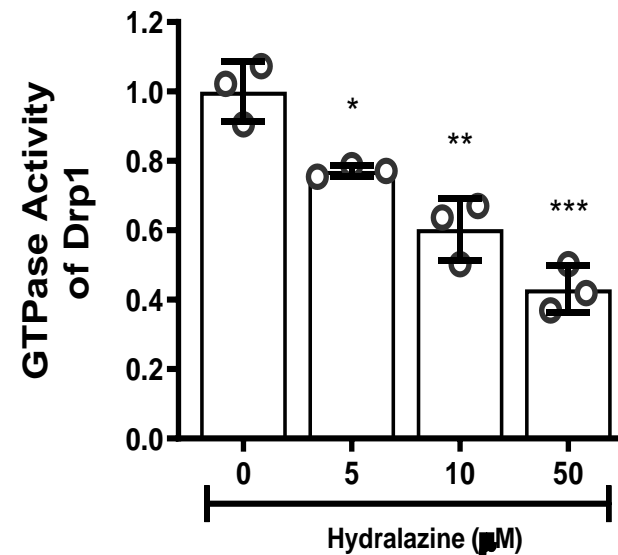
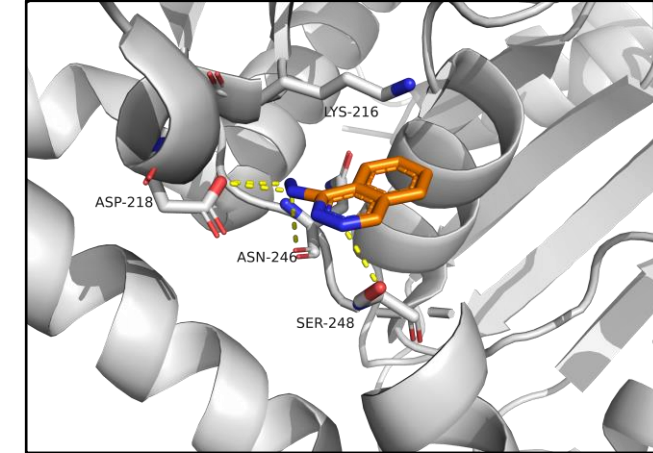
HTS (1280 FDA small molecules) identified **hydralazine** to be potent inhibitor of mito fission.

Molecular docking studies: hydralazine binds to GTPase domain of Drp1 and inhibits its activity.

Surface plasmon resonance binding studies: hydralazine binds to Drp1.

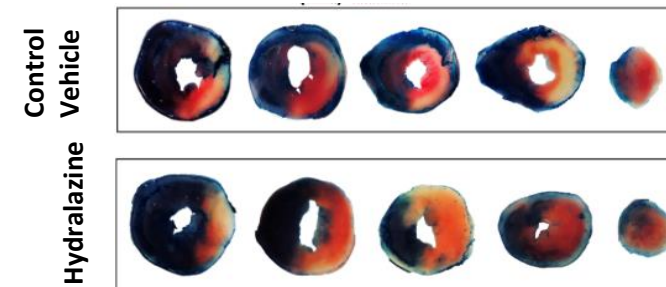
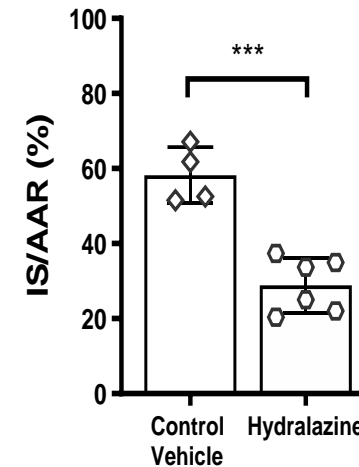
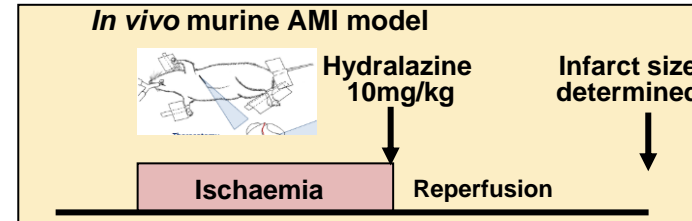
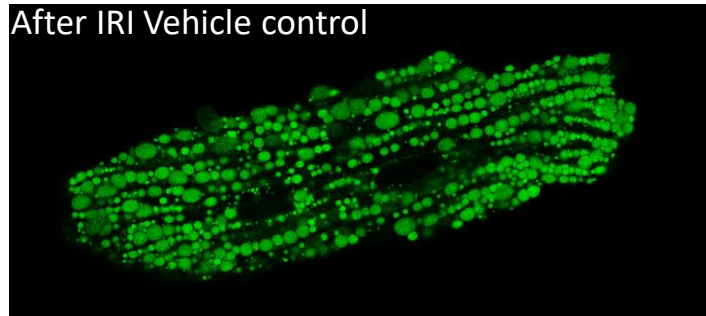
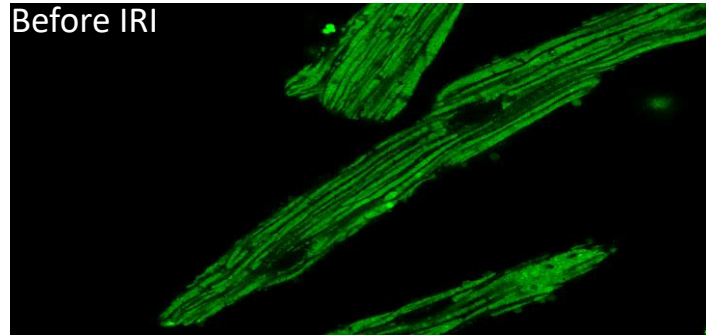


Hernandez....Hausenloy
J Cell Mol Med 2020



Kalkhoran....Hausenloy Cardiovasc Res 2021

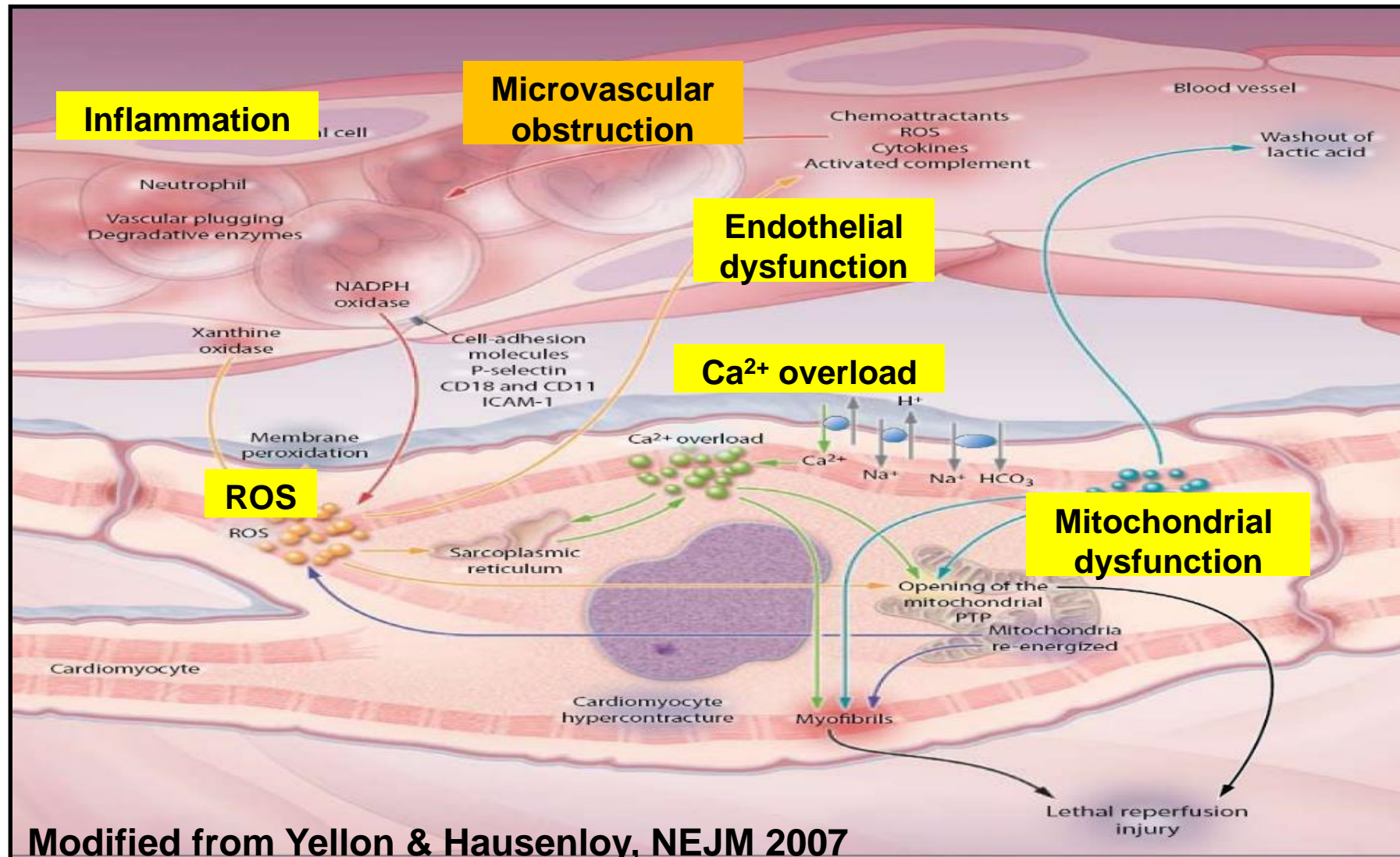
Hydralazine inhibits mitochondrial fission and reduces MI size



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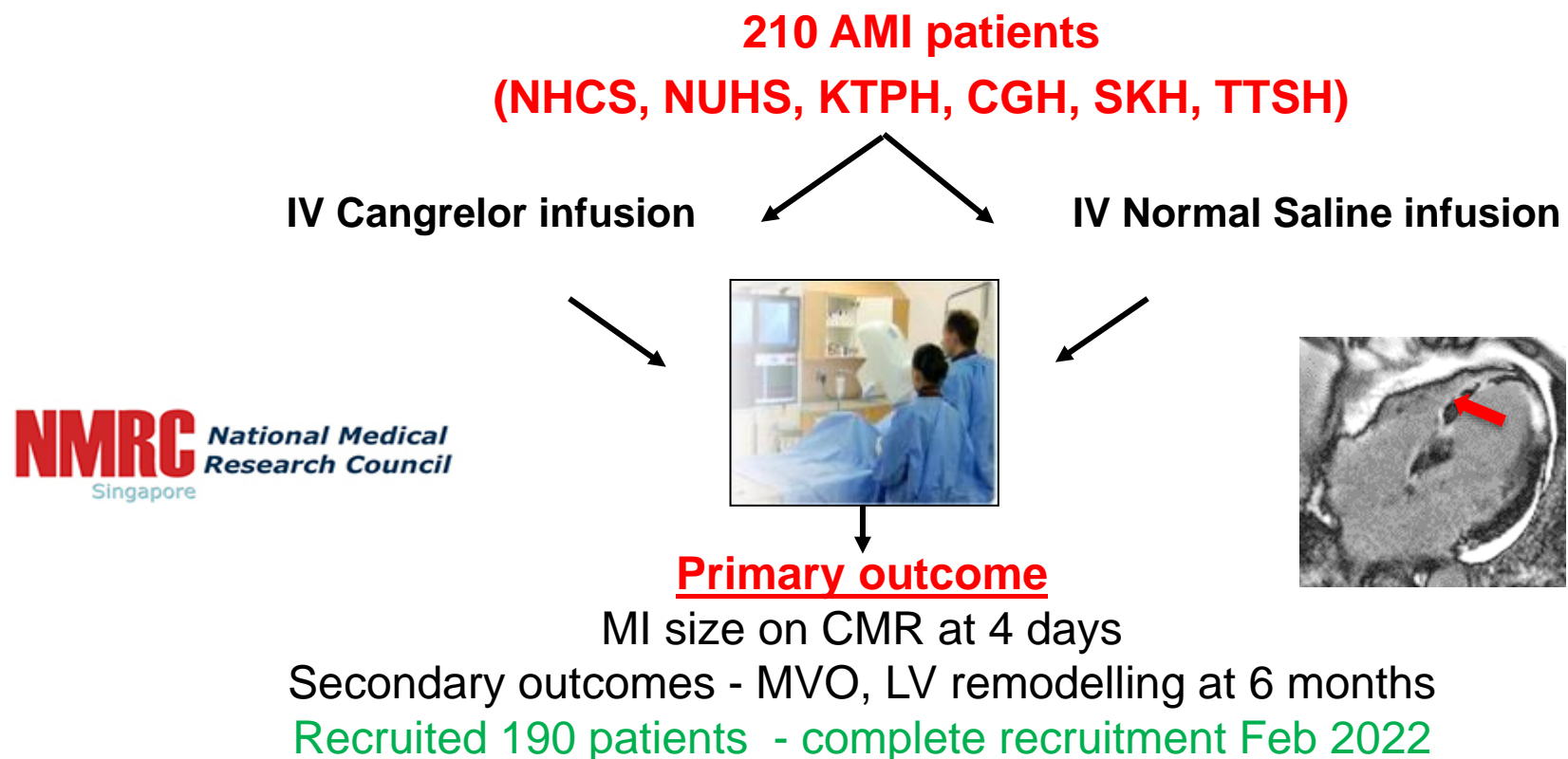
What causes acute myocardial ischemia/reperfusion injury ?



PITRI trial: Platelet Inhibition to Target Reperfusion Injury

Oral platelet inhibitors do not completely inhibit platelet activity in STEMI patients. Cangrelor IV P2Y12 platelet inhibitor with rapid onset of action:

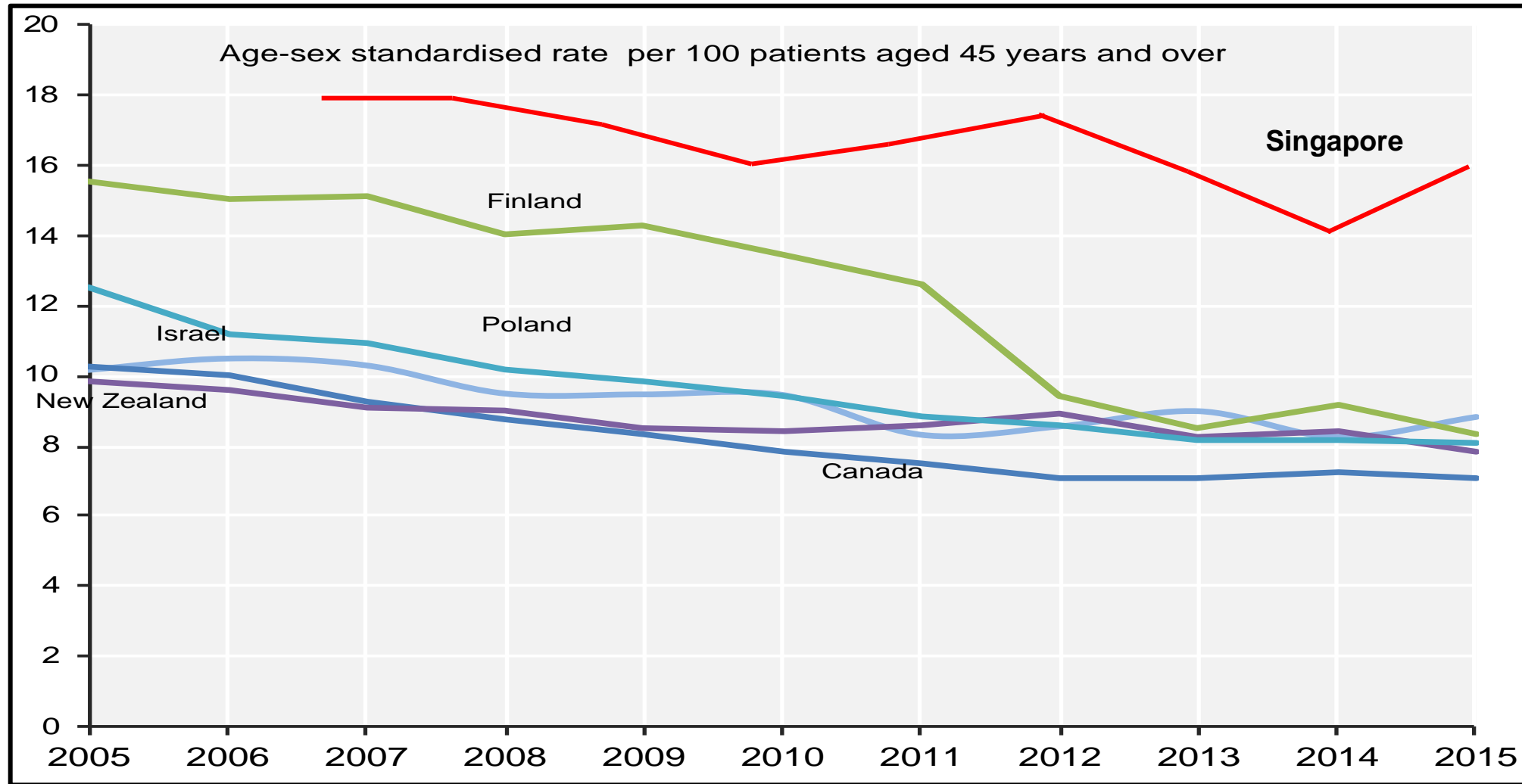
- (1) **Platelet**: maximum platelet inhibition at angioplasty, thereby preventing MVO.
- (2) **Cardiomyocyte**: reduces MI size in animal IRI models.



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Problem: High 30-day AMI mortality in SG



Source: OECD Health Statistics 2017

Solution: AMI-HOPE to improve outcomes



AMI-HOPE program

- MOH HSDP-funded cross-cluster program (7 hospitals and their polyclinics) to improve AMI outcomes.
- Recruit 4000 AMI patients (Drug compliance and Death/Hospitalisation).



Source: OECD Health Statistics 2017

AMI-HOPE: Allied health and digital technology to improve post-AMI outcomes

In-hospital phase

Root cause of problem

Suboptimal use of post-AMI medication and rehabilitation.

AMI-HOPE solution

AHPs to stratify patients according to risk and ensure patients started on post-AMI medication and cardiac rehabilitation.



Early post-discharge phase

Root causes of problem

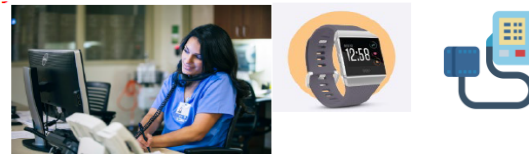
Poor compliance and no uptitration of post-AMI meds.

Variable first follow-up at 2-3 months, and infrequent visits.

AMI-HOPE solution

AHPs to see all patients at 2 weeks and follow-up remotely for 3-6 mths.

Use telehealth (VSM) to maintain compliance and uptitrate post-AMI medication.



Transition to primary care

Root causes of problem

Occurs at 12 mths or never happens – remain in SOC.

Inadequate hand-over from hospital to primary care resulting in poor compliance with post-AMI medication.

AMI-HOPE solution

AHPs to coordinate transition at 3-6 mths depending on patient risk, and ensure formal hand-over.

Wearable-enabled self-care in community.



MOHT

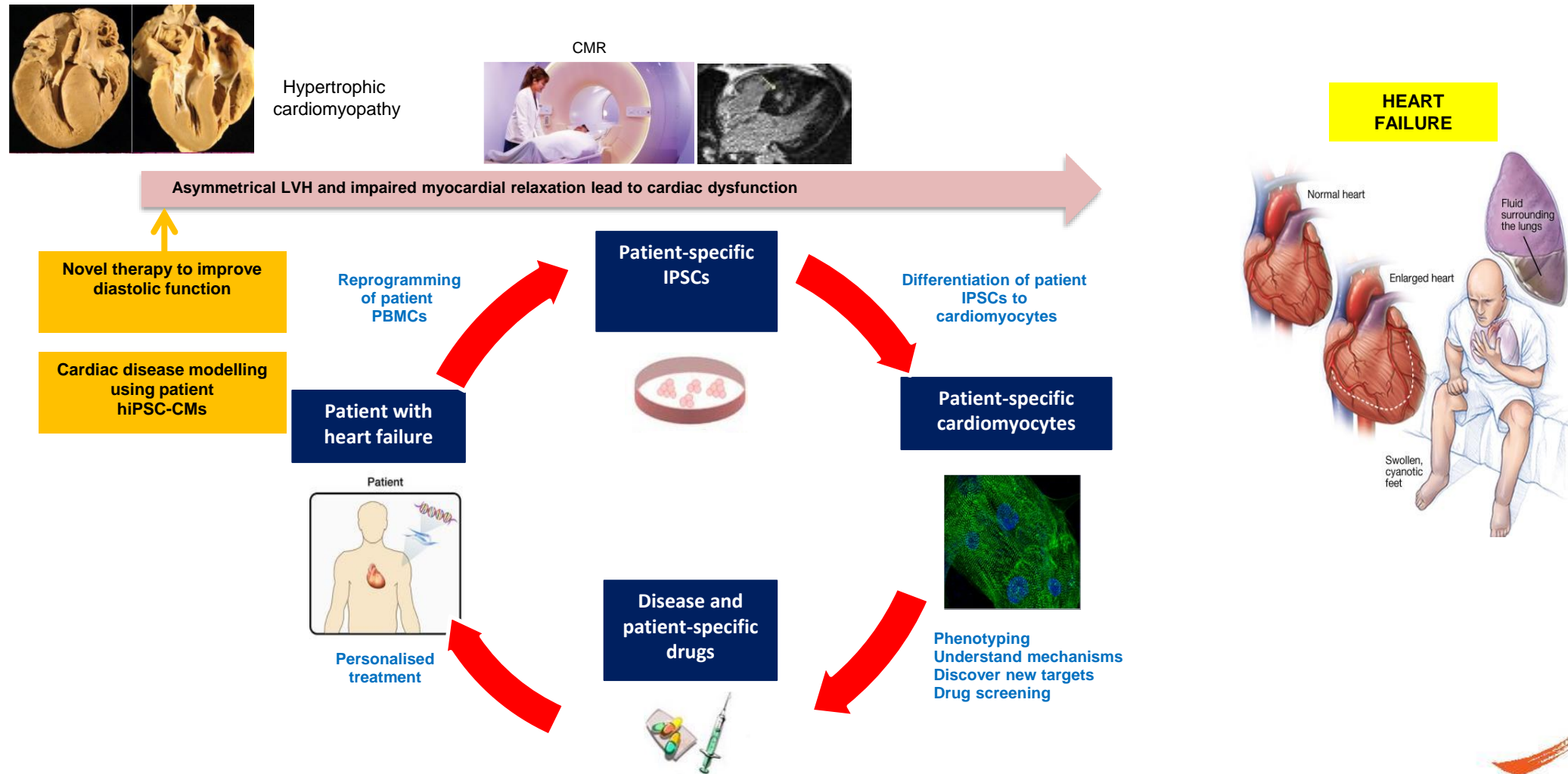
MOH OFFICE FOR HEALTHCARE TRANSFORMATION



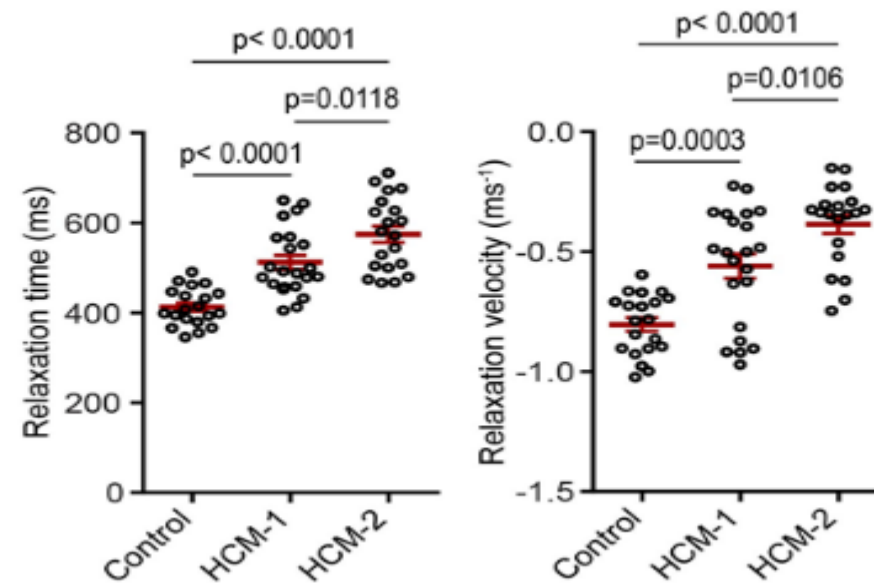
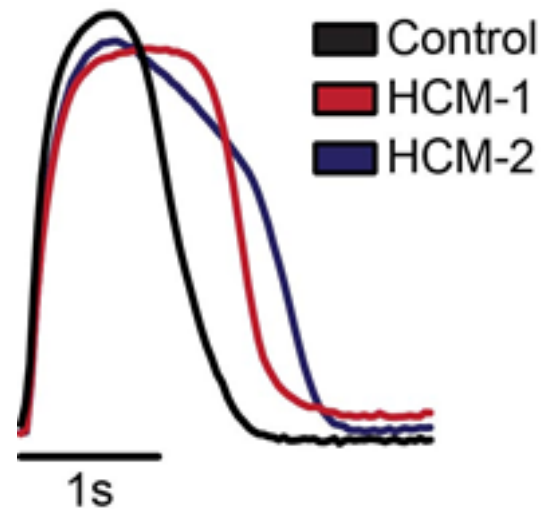
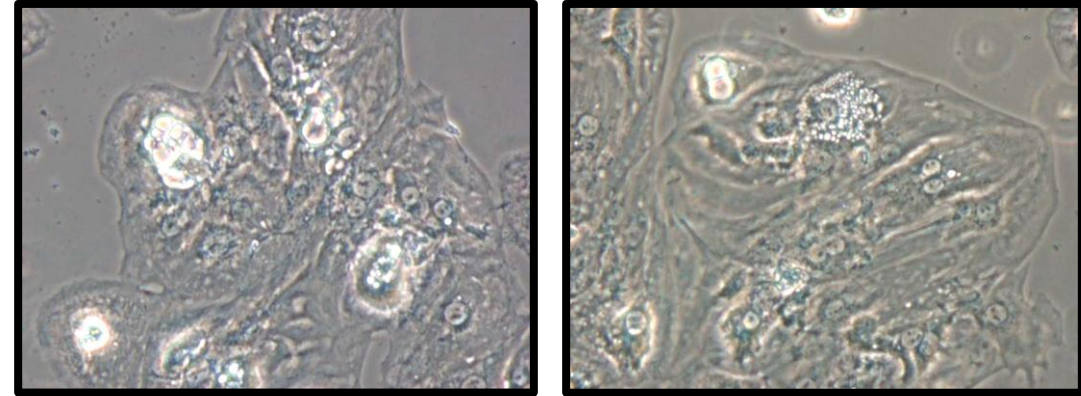
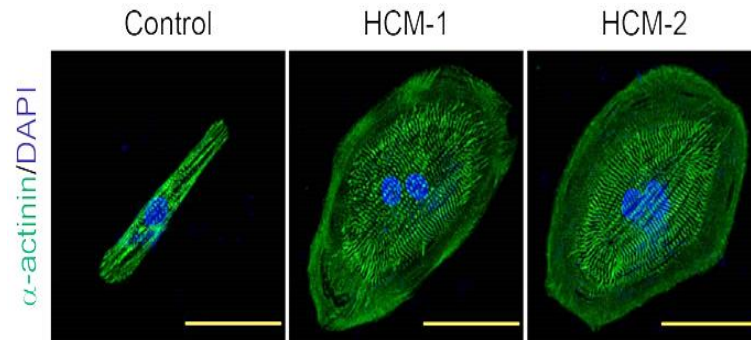
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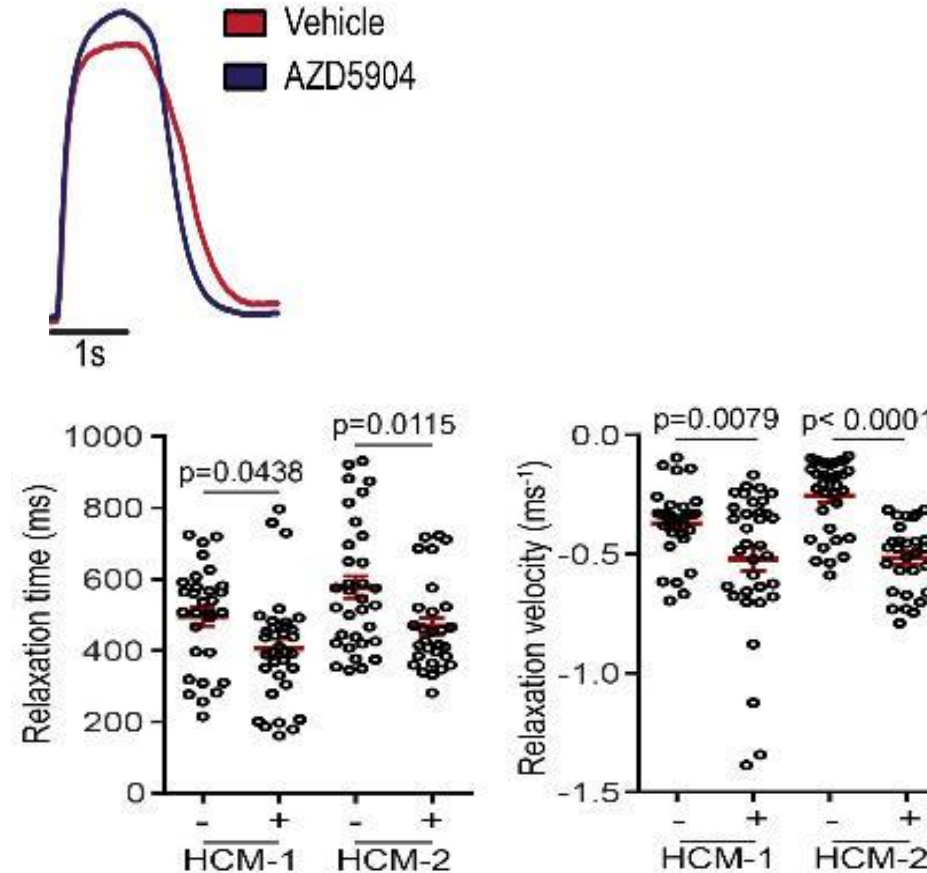
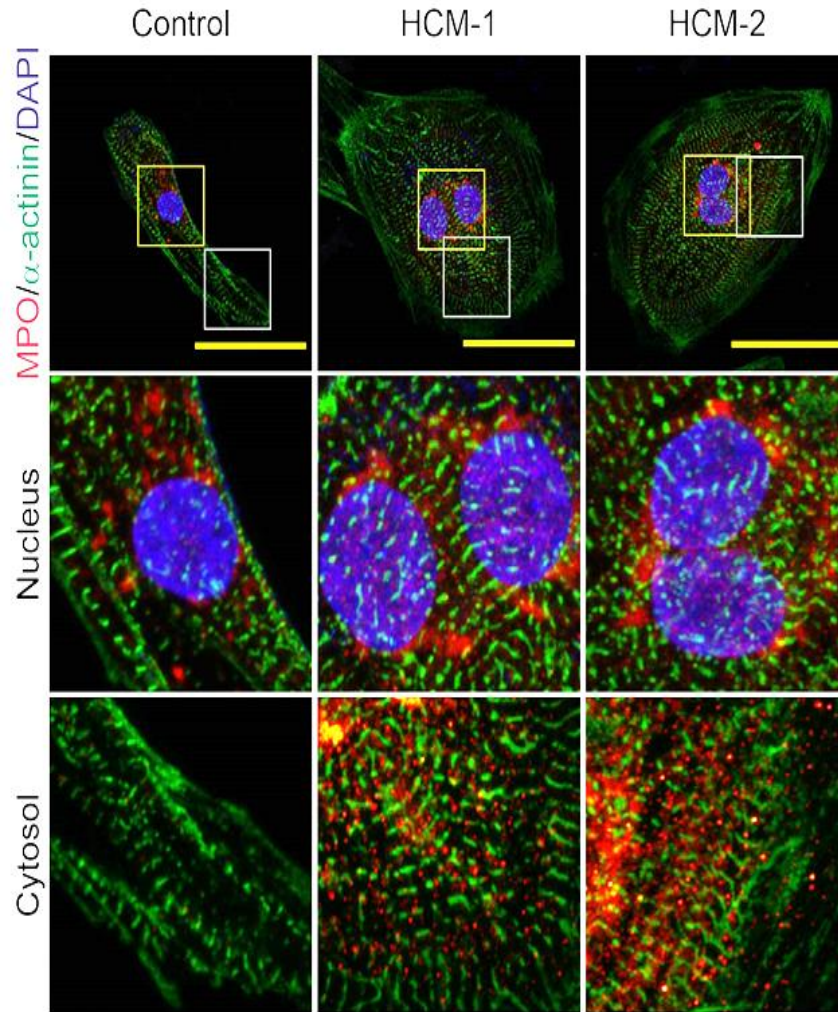
Using human iPSC-derived CMs to model cardiac disease and discover new treatments



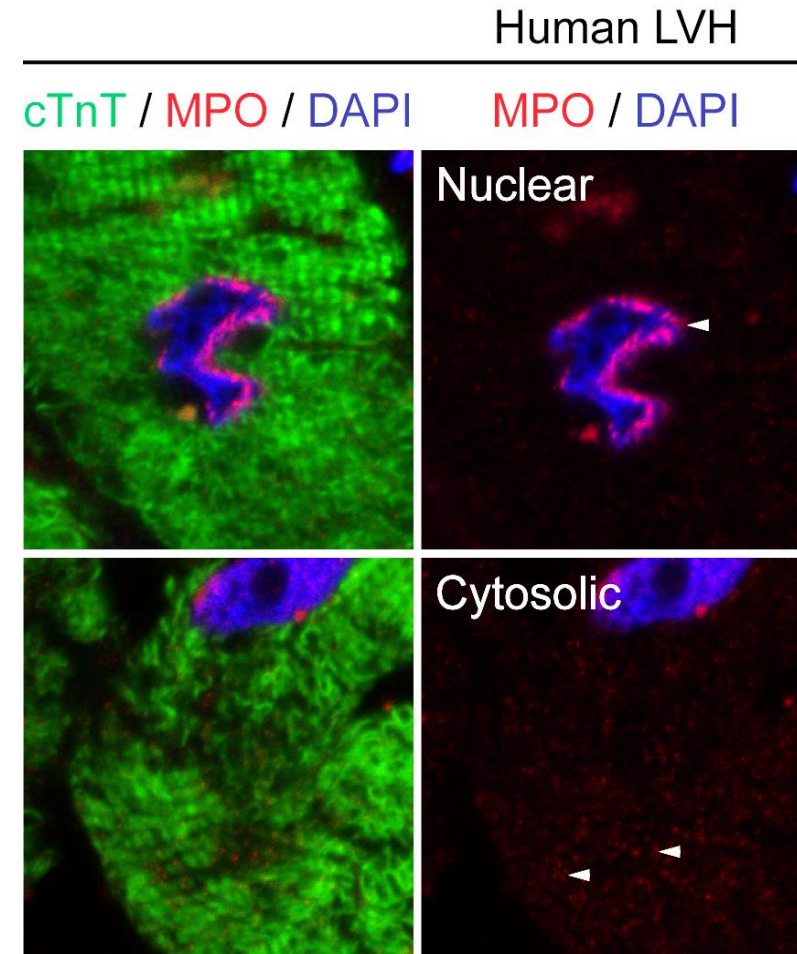
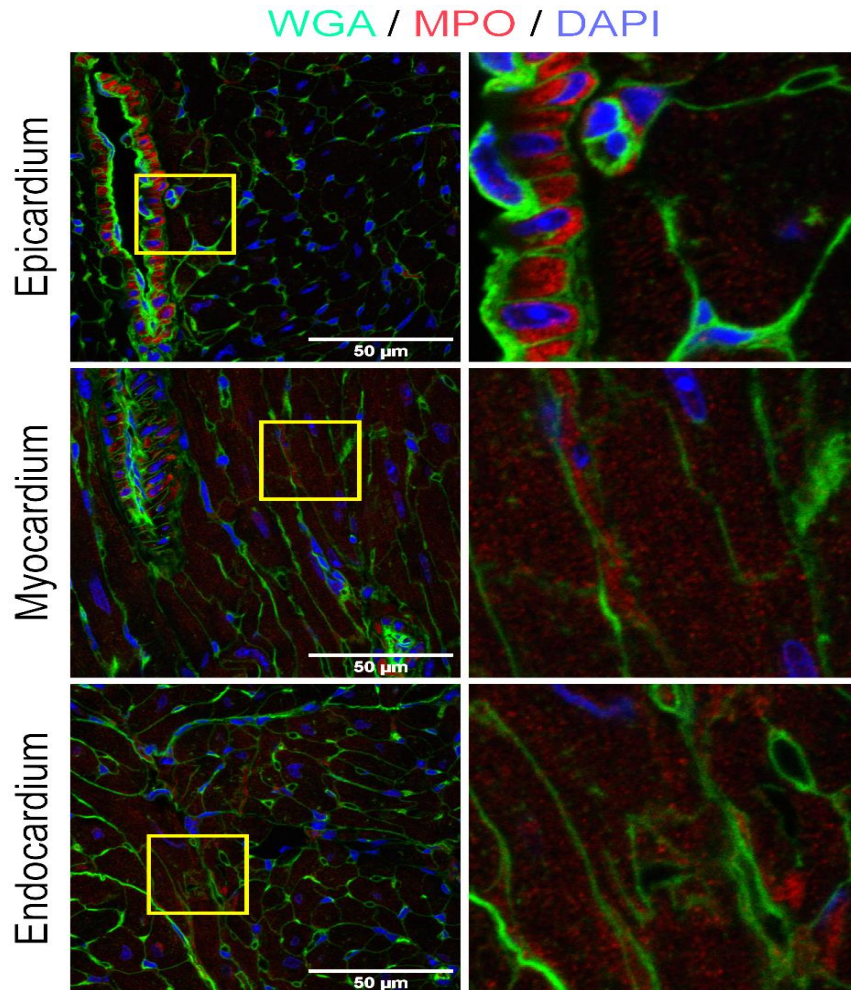
IPSC-HCM cardiomyocytes display hypertrophy and exhibit impaired relaxation



MPO expressed in iPSC cardiomyocytes and MPO inhibition alleviates relaxation defect



Cardiomyocyte MPO is present in the adult mouse and human heart



Ramachandra...Hausenloy Unpublished

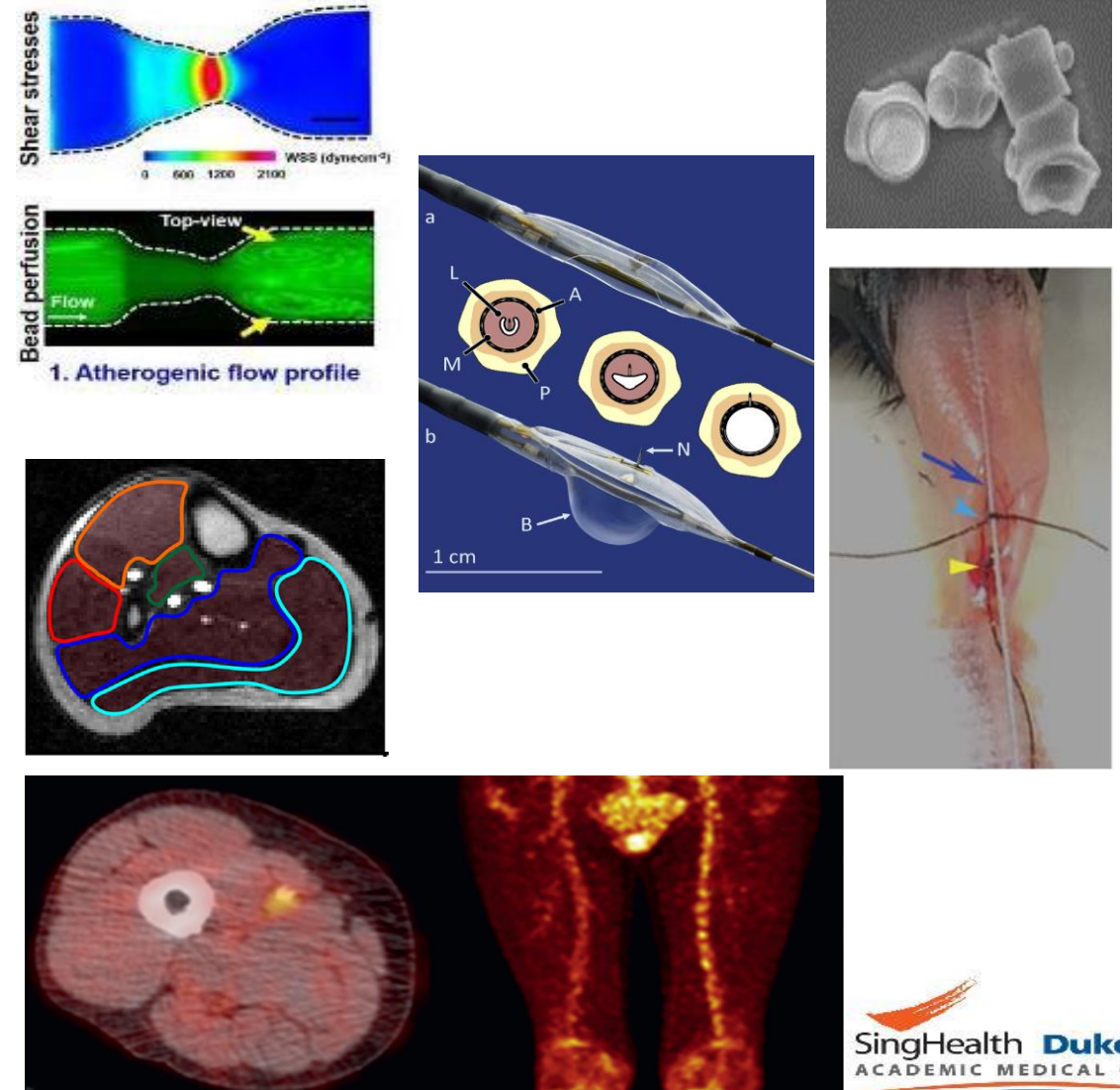
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Vascular Protection – to prevent atherosclerosis

Preventing atherosclerosis progression and restenosis in DM PAD (NRF CRP REDUCE-PAD program) - Duke-NUS, NHCS, NUS, NTU, NUHCS, KTPH

1. **Discovery:** Sc-RNAseq of vascular tissue from DM mice/pig/PAD patients.
2. **Validation:** Test IL-11Ab and LOX-1Ab in DM mice PAD models and human vessels on a chip.
3. **Delivery:** Design novel NPs to deliver IL-11Ab into vasculature to prevent restenosis in DM pig PAD model.
4. **Clinical:** Cross-cluster trial to test whether LOX-1Ab can reduce plaque inflammation and improve limb perfusion in DM PAD patients.



Summary and Conclusions

- Hydralazine inhibits mitochondrial fission – potential for repurposing as treatment for AMI.
- Cross-cluster **PITRI trial** (NMRC CTG) currently testing whether optimising platelet inhibition using cangrelor is beneficial in STEMI patients.
- Cross-cluster **AMI-HOPE study** (MOH HSDP) will test whether optimising post-AMI secondary prevention using AHP-enabled digital technology can improve AMI outcomes.
- Using **human iPSC-CMs** we have identified cardiomyocyte MPO as a novel treatment target to improve myocardial relaxation in HCM patients – MPO inhibitors already in clinical testing.
- Multi-institution **REDUCED-PAD program** (NRF CRP) will test whether LOX-1b and IL-11Ab therapies can prevent atheroma progression and reduce post-angioplasty stenosis in DM PAD.

Acknowledgements

Duke-NUS/NHCS, Singapore

Siavash Kalkhoran
Chrishan Ramachandra
Sauri Hernandez-Fernandez
Myu Mai Ja Kp ('Marie')
Shengjie Lu
Ying-Hsi Lin ('Alvin')
Gustavo Crespo
Yu Fan
En Ping Yap
Shuo Cong
Xiaomeng Wang
Aishwarya Prakash
Jasper Chua
Ariel Ying
Jun Chong

Melbourne, Australia

Max Lim
Jessica Holiens

