



Discovery of cardioprotective prokineticin receptor agonist: anti-cancer drug induced cardiotoxicity

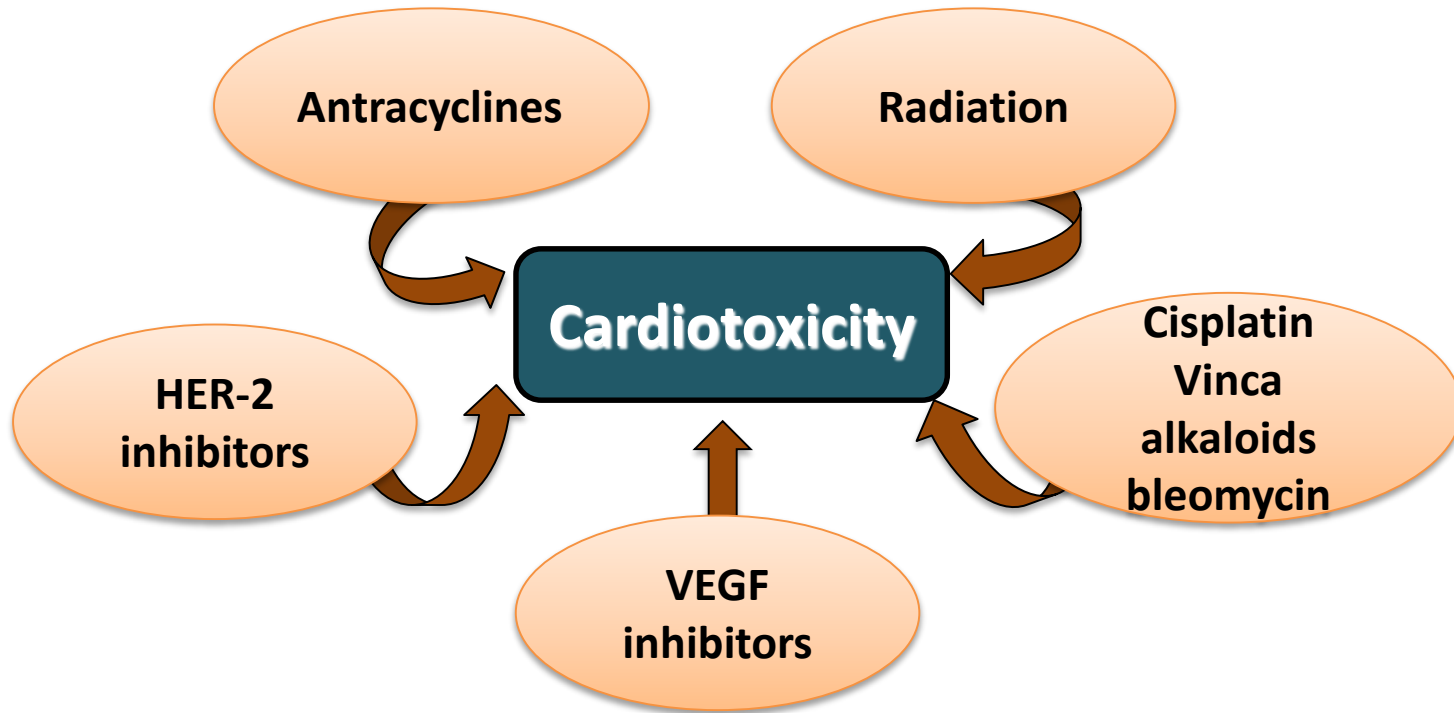
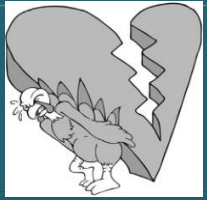
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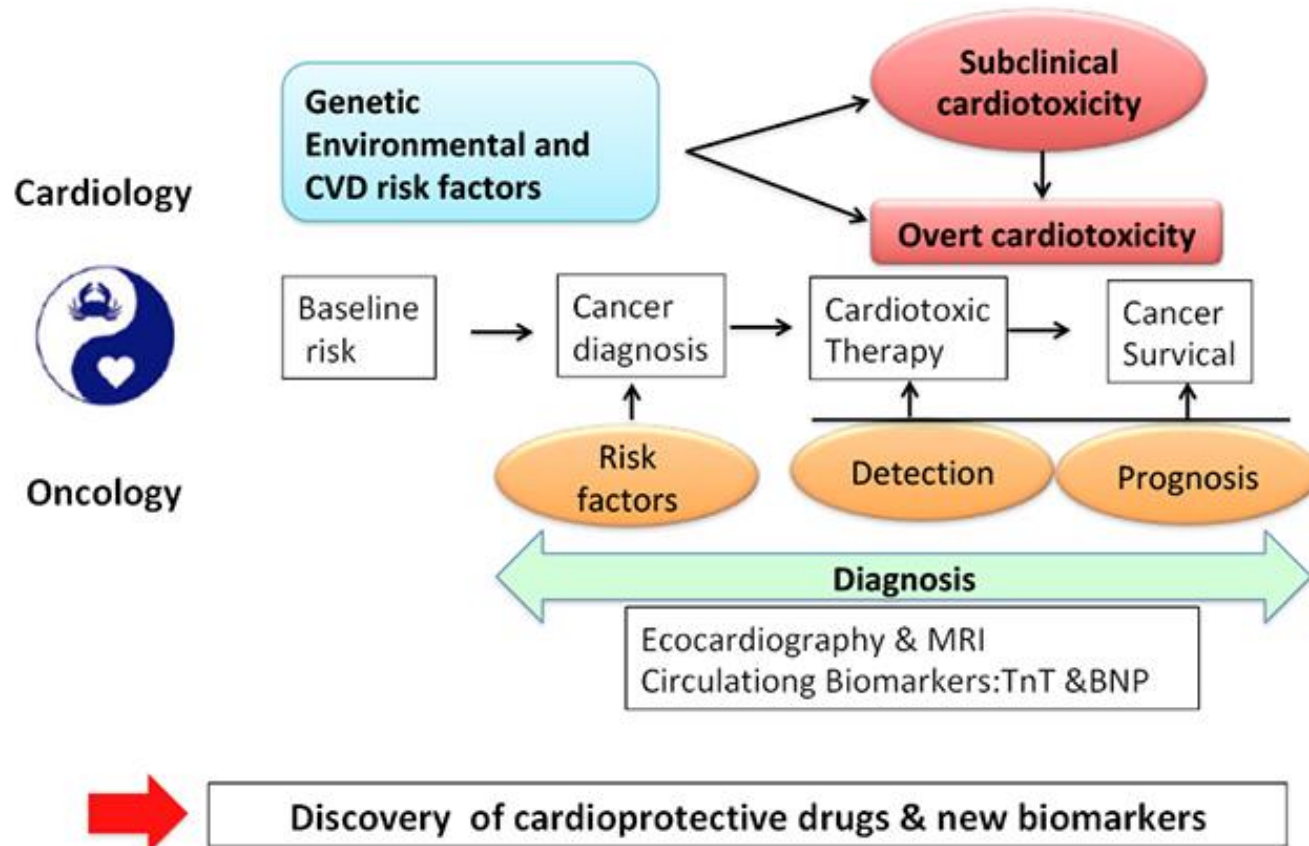
UMR7242, ESBS

AnP, 30 May, 2018

Most of the anticancer treatments induce cardiotoxicity



Cardiovascular side effects of anti-cancer treatments



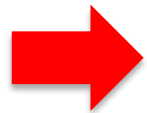
Dexrazoxane is the only FDA & EMA approved cardioprotective agent to prevent anticancer drug-induced cardiotoxicity



➔ **On TARGET**-----Treatment of Cardiotoxicity

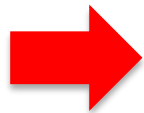
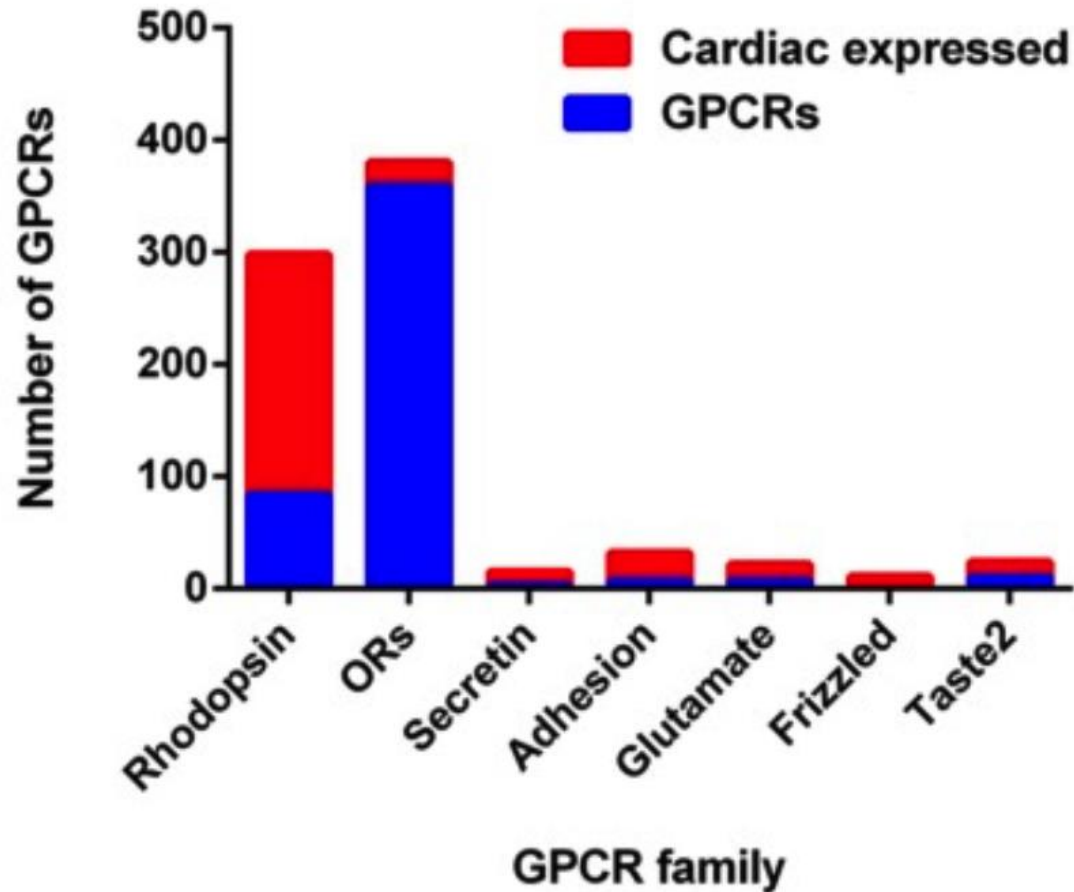
➔ **Off TARGET**----Tumor development

European Medicines Agency forbidden its uses in children and restricts in adults



GPCRs are the target of 40% of clinically used medicals

GPCRs in heart



Prokineticin receptors in heart

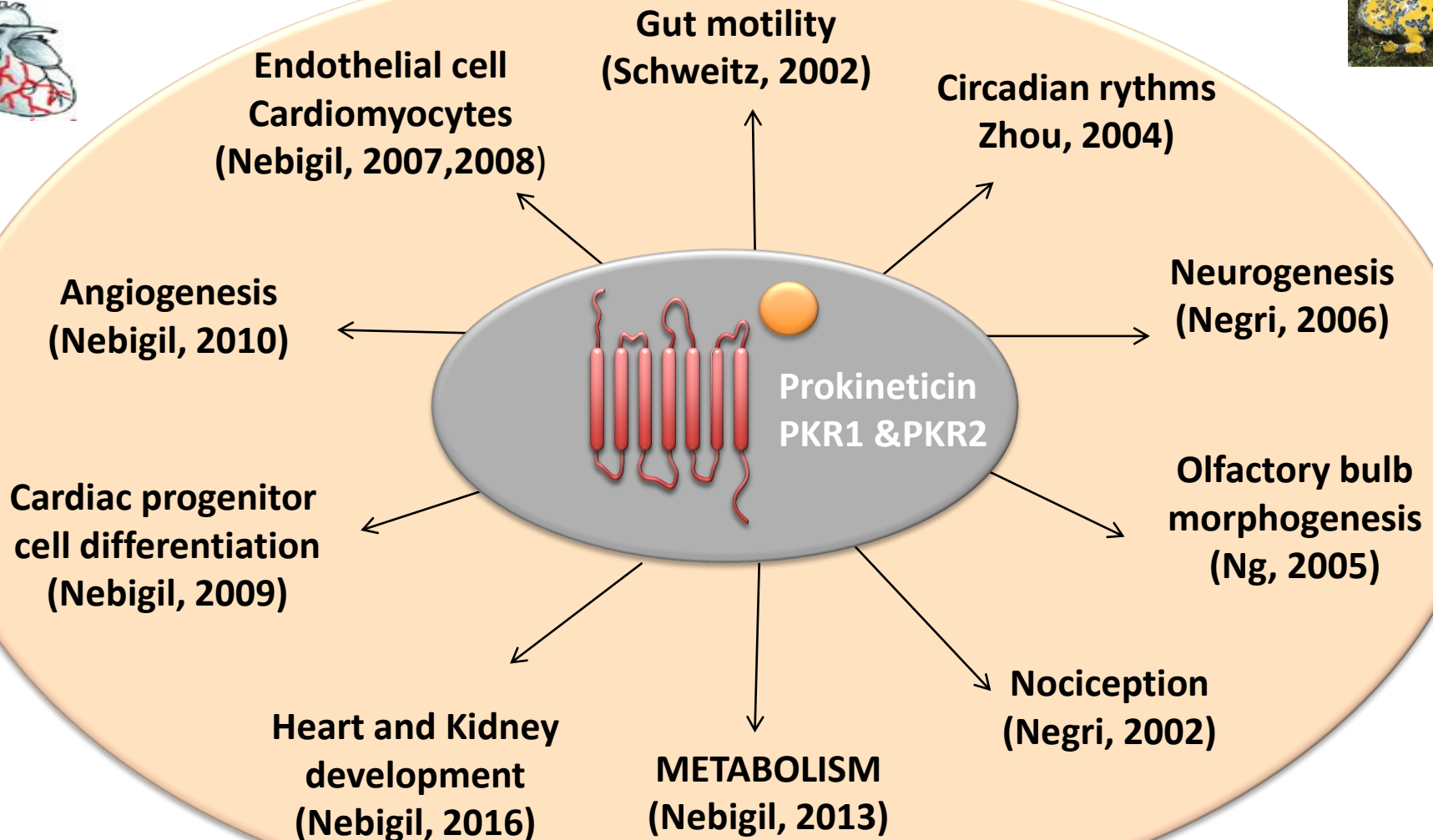
WHAT ARE PROKINETICINS?

Prokineticins are hormones discovered in 2002

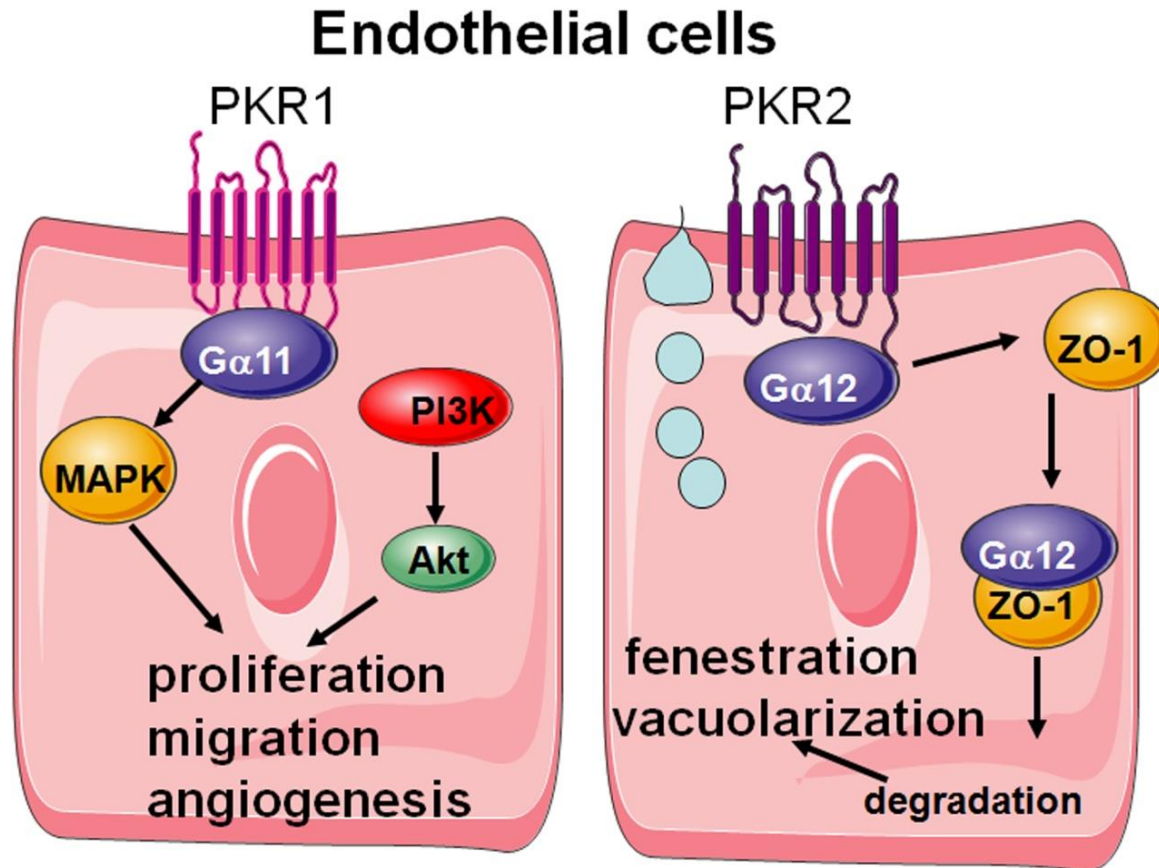
PK1 (EG-VEGF)



PK2 (Bv8)



Prokineticin signaling in cardiac endothelial cells

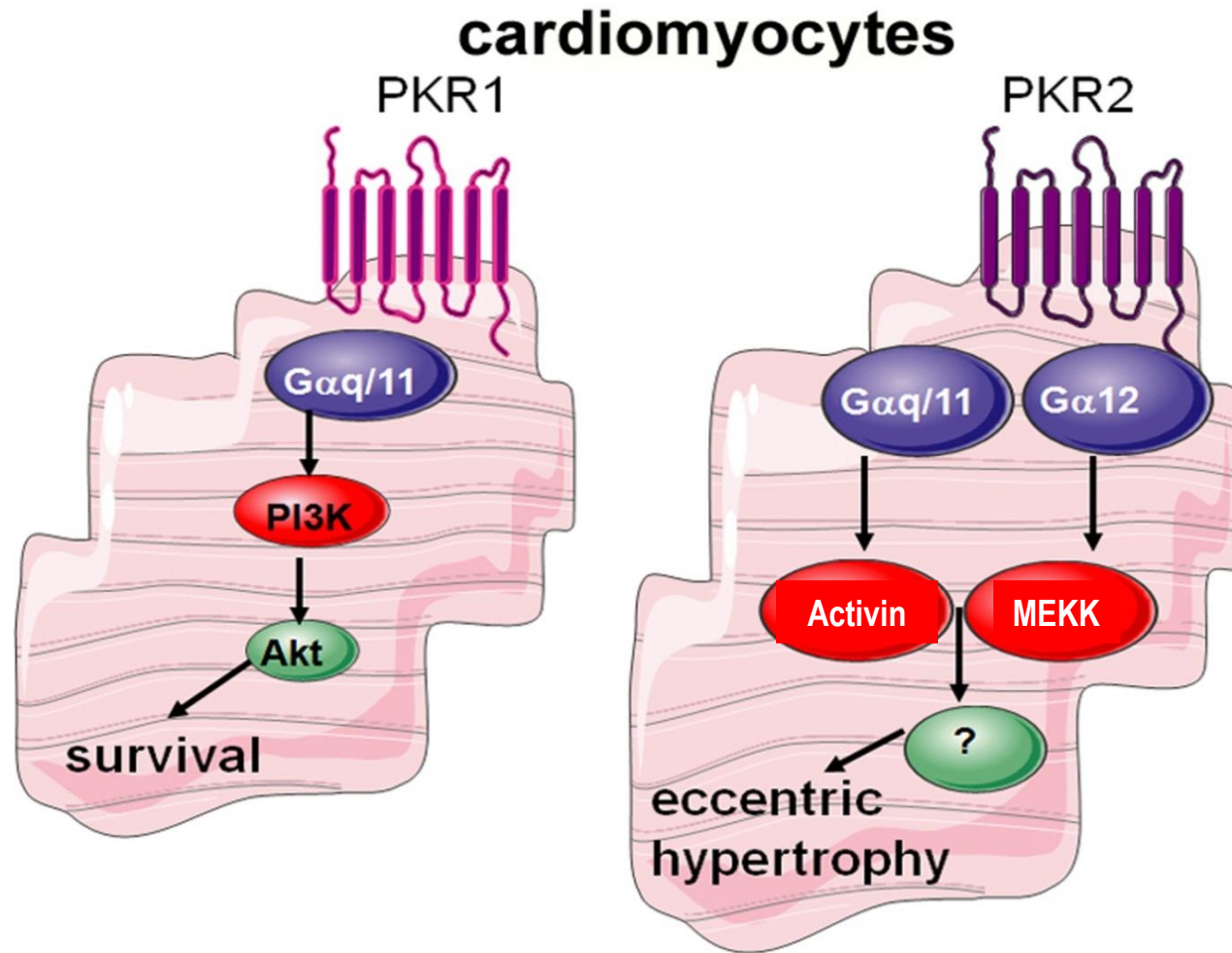


Urayama et al. FASEB J. 2007

Guilini et al. Am. J. Physiol. 2010

Dormishian, JAHA. 2013

Prokineticin signaling in cardiomyocytes

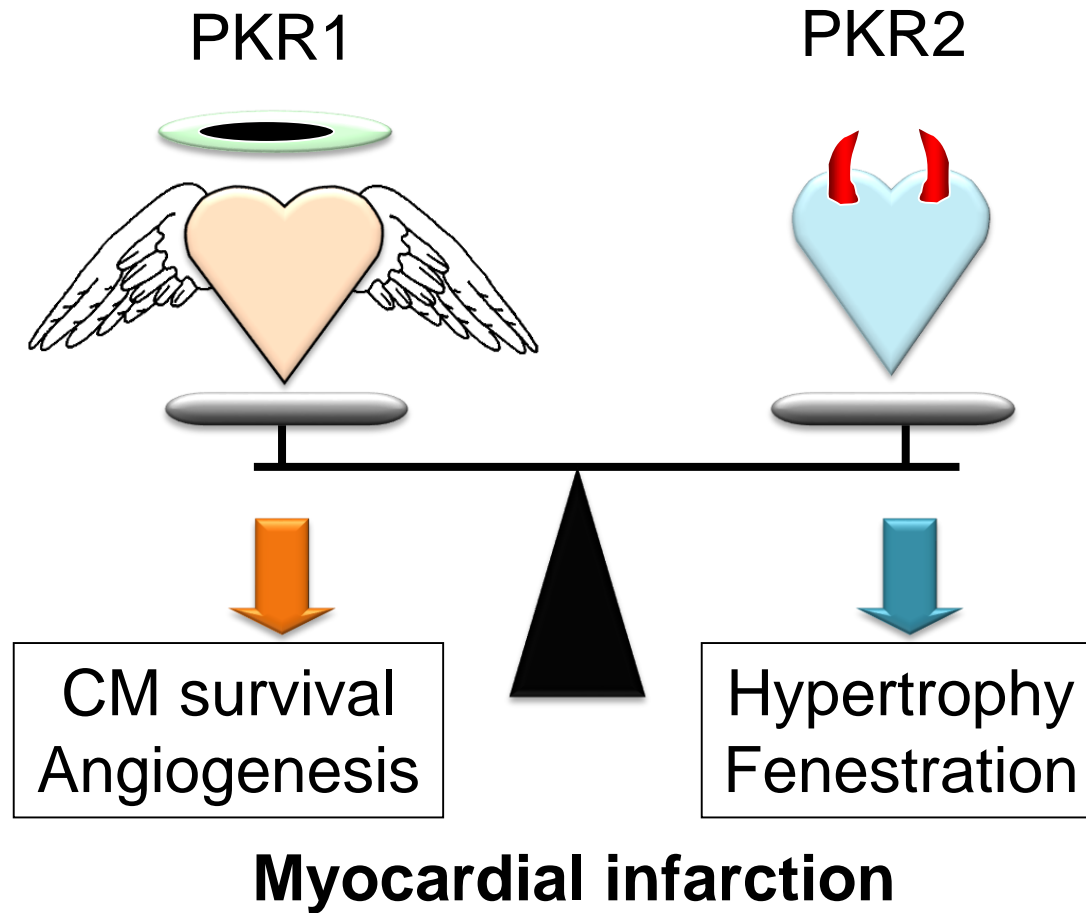


Urayama et al. FASEB J. 2007

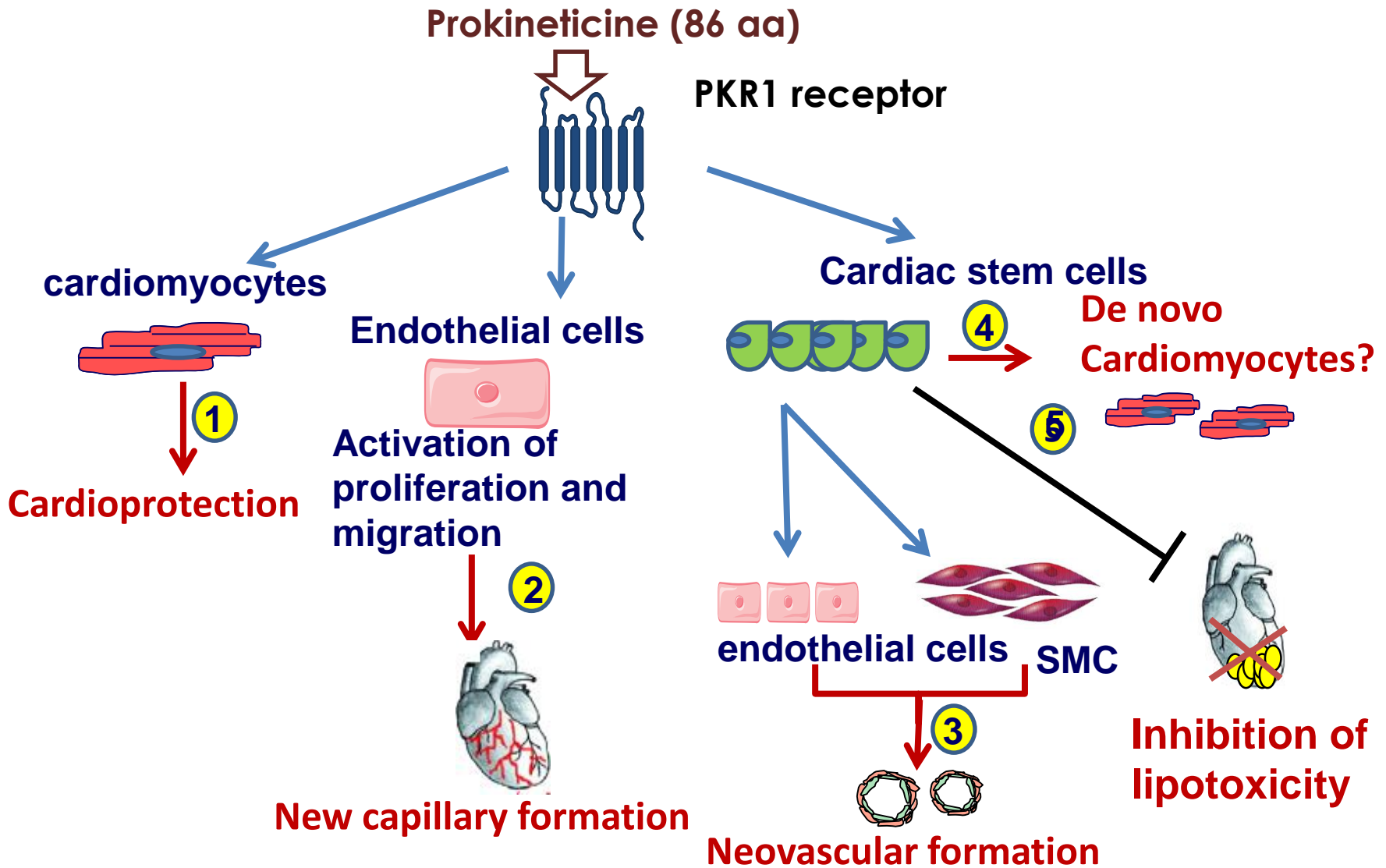
Boulberdaa, ATVB. 2011

Urayama et al. Cardiovas. Res., 2009

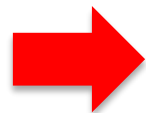
A balance between angel and evil sides of prokineticins



Why Prokineticin/PKR1 is an ideal candidate to regenerate damaged heart



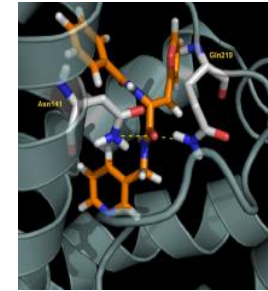
**Targeting PKR1 can be a novel approach
to combat
cardiovascular diseases**



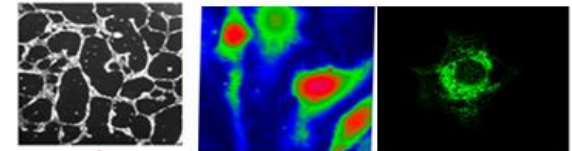
DRUG Discovery program

Drug Discovery: Identification of first PKR1 agonist

In silico identification of putative PKR1 ligands (A. Tafi, Sienna University)



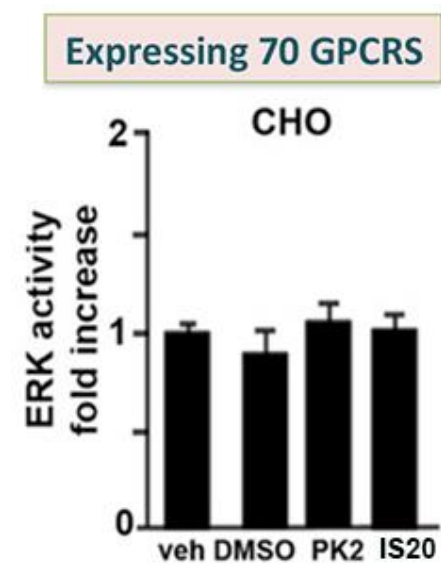
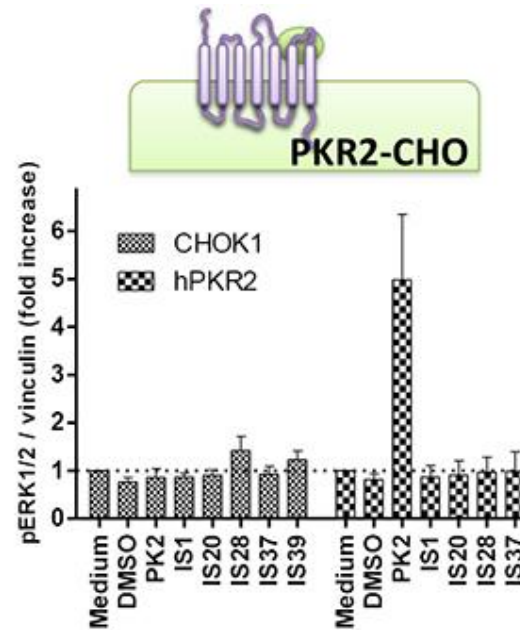
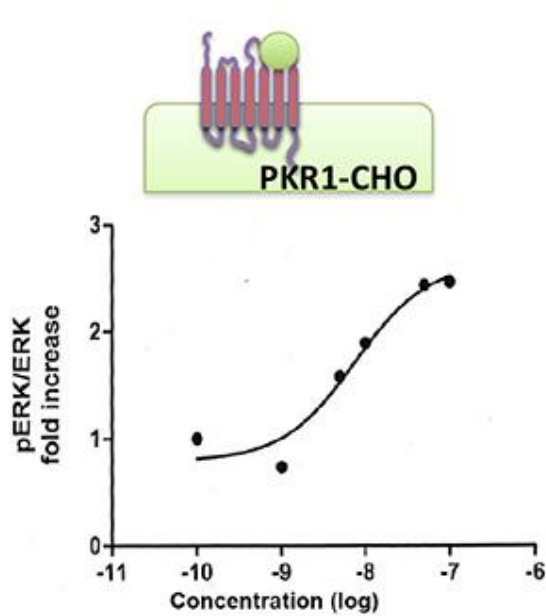
In vitro pharmacological identification of PKR1 agonists
Angiogenesis, calcium releasing,
internalization (Nebigil)



Synthesis of analogues that display enhanced
pharmacological properties
(Désaubry, Strasbourg Faculty of Pharmacy, UdS, Illkirch)

In vivo evaluation in preclinical murine models of MI and
cardiotoxicity (Nebigil)

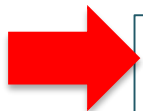
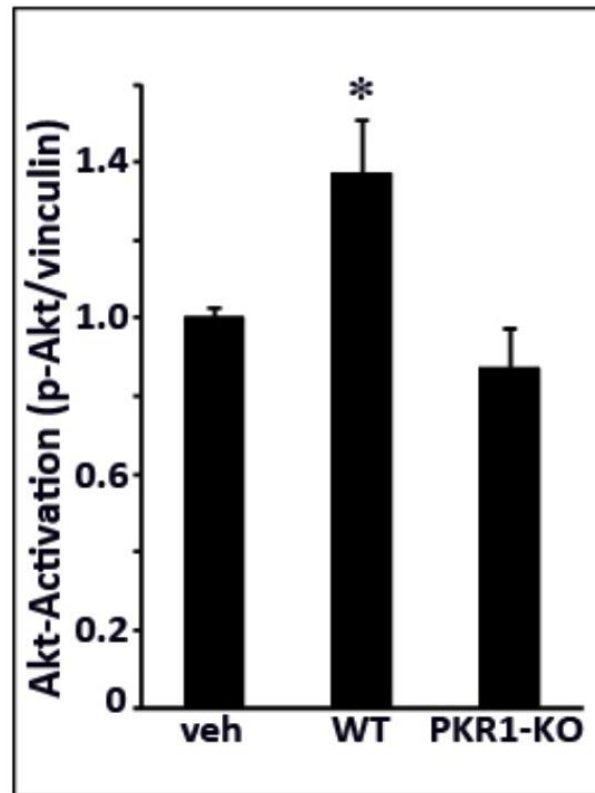
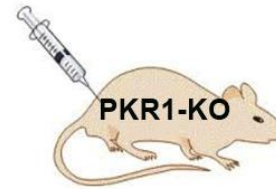
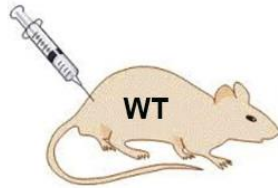
Identification of first PKR1 agonist IS20



IS20 has no effect without PKR1

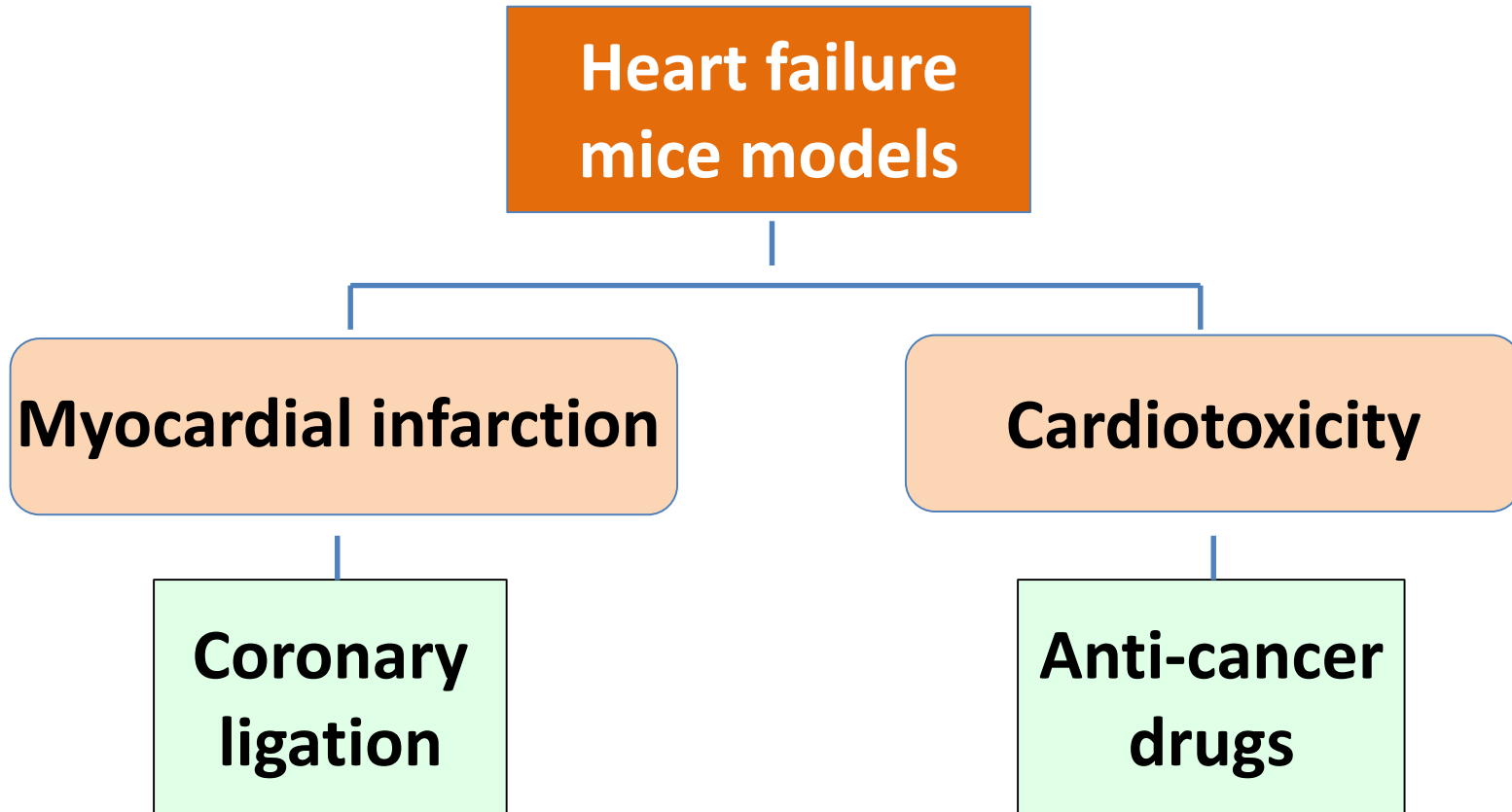
Biomarker analyses

IS20
0.5mg/kg



IS20 is active in vivo and utilizes PKR1

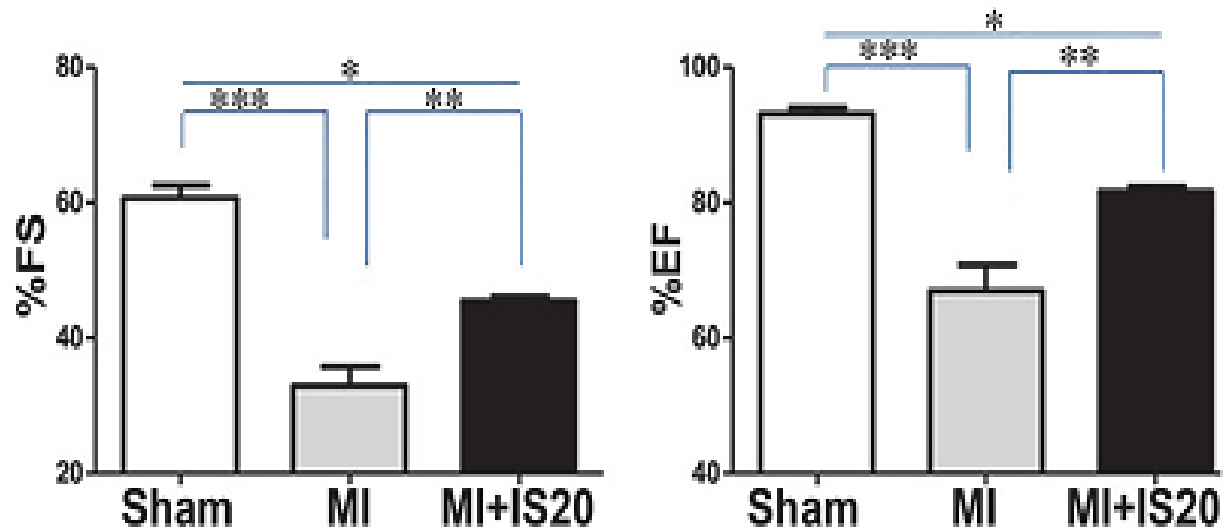
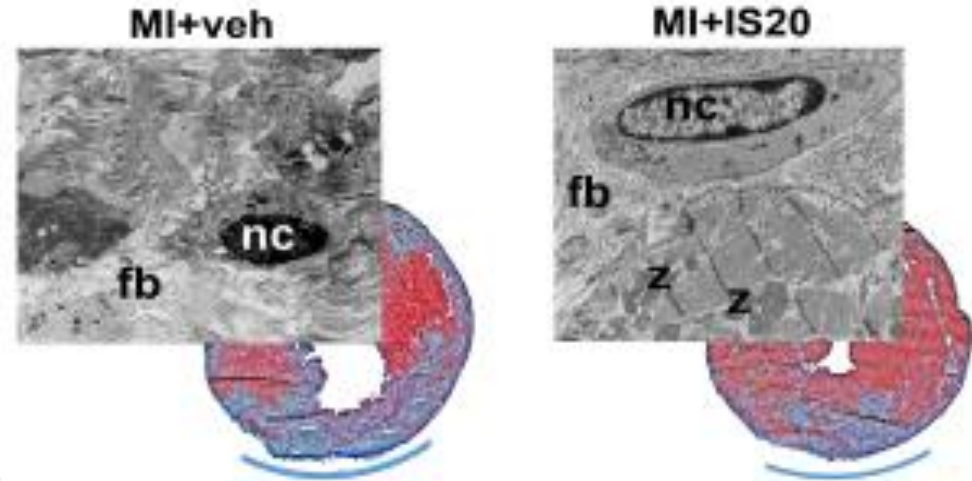
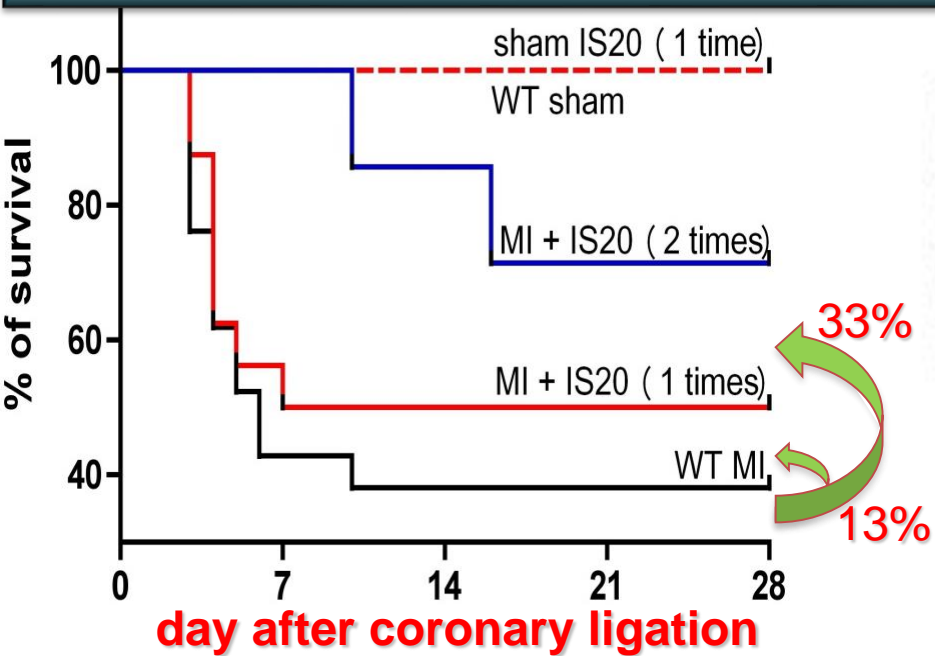
Role of IS20 on heart failure



Gasser et al., PlosOne 2015

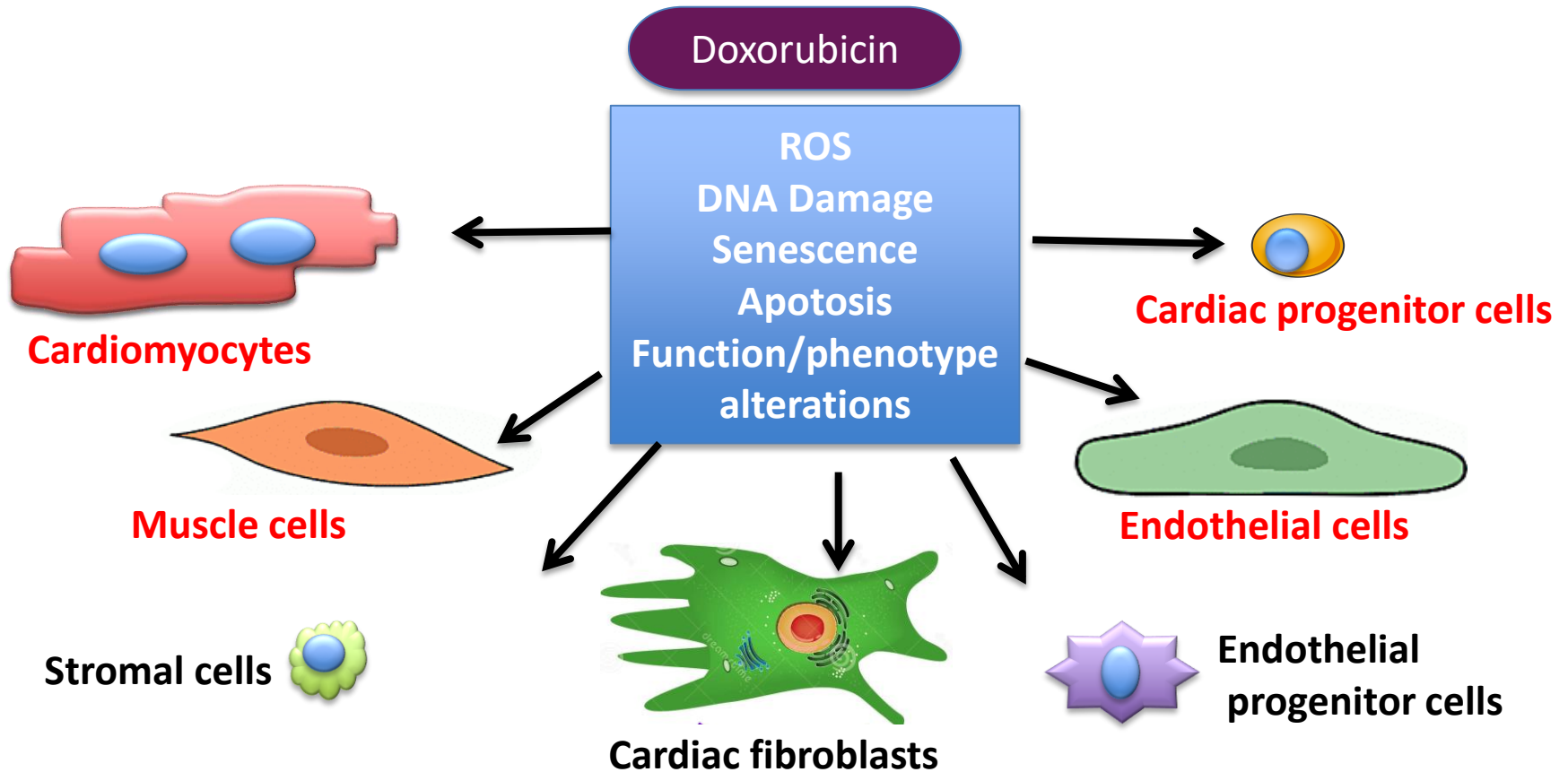
Gasser et al., Submitted 2018

IS20 improves survival rate and heart function after MI

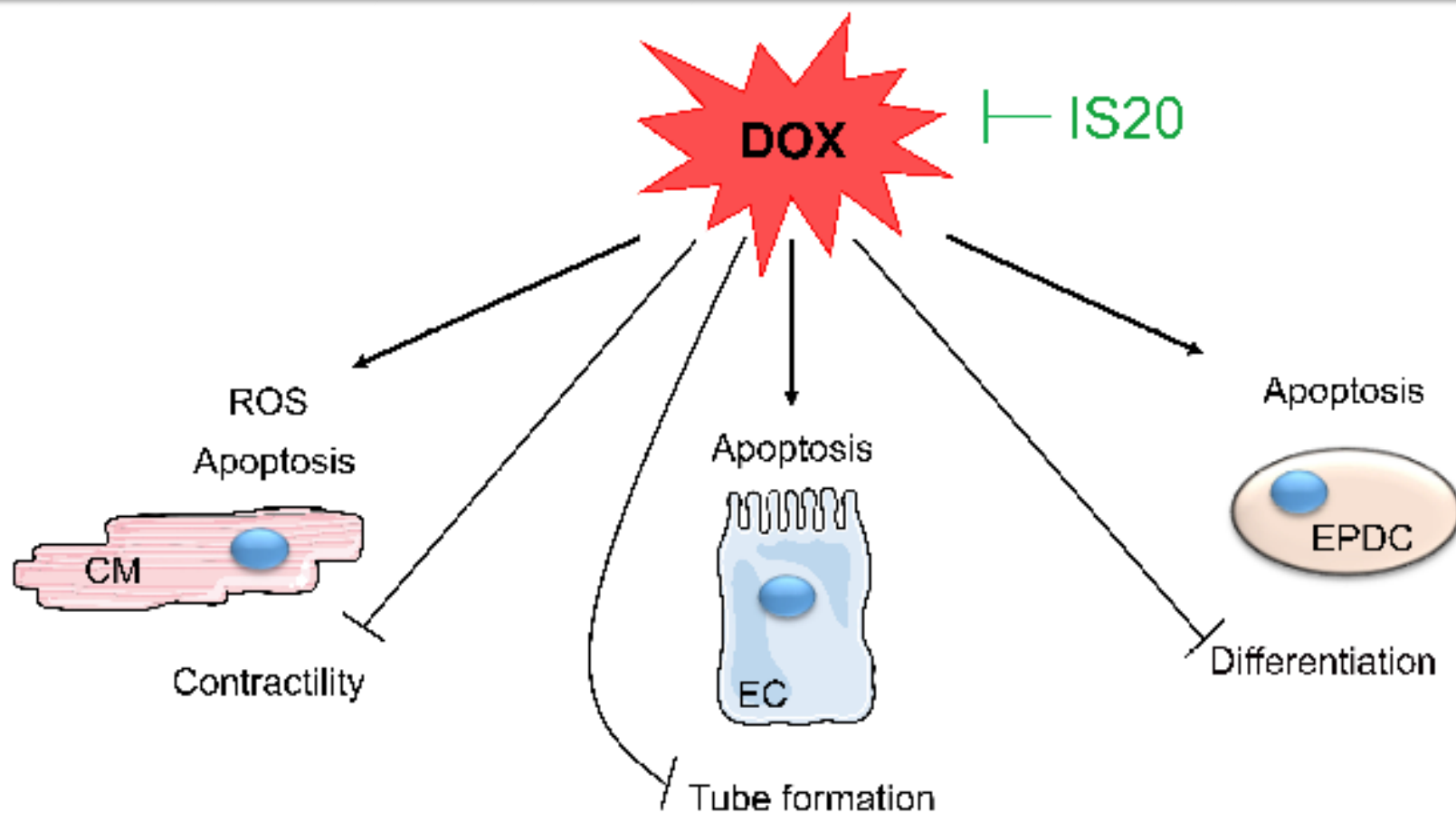


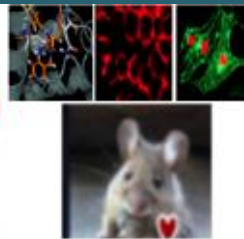
Doxorubicin-Induced cardiotoxicity : Affected cells

If IS20 protects cardiac cells against DOX-induced CT



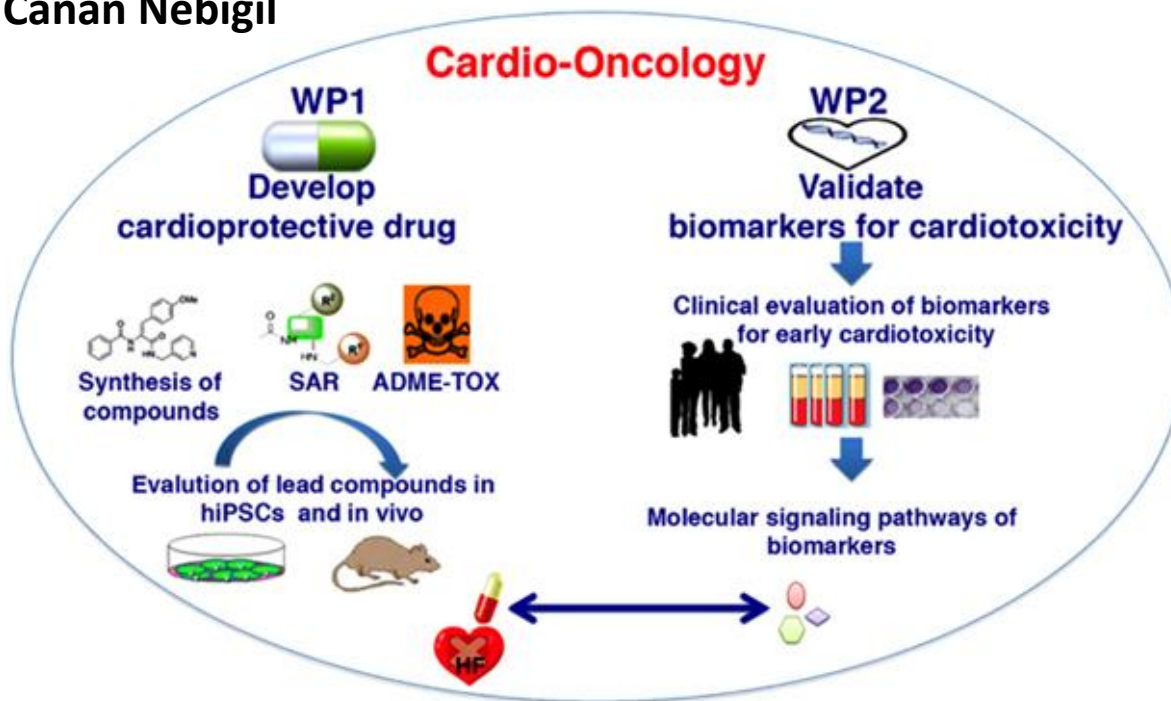
IS20 protects detrimental effect of DOX on cardiomyocytes, endothelial cells and epicardial progenitor cells without altering anti-tumor effects of DOX



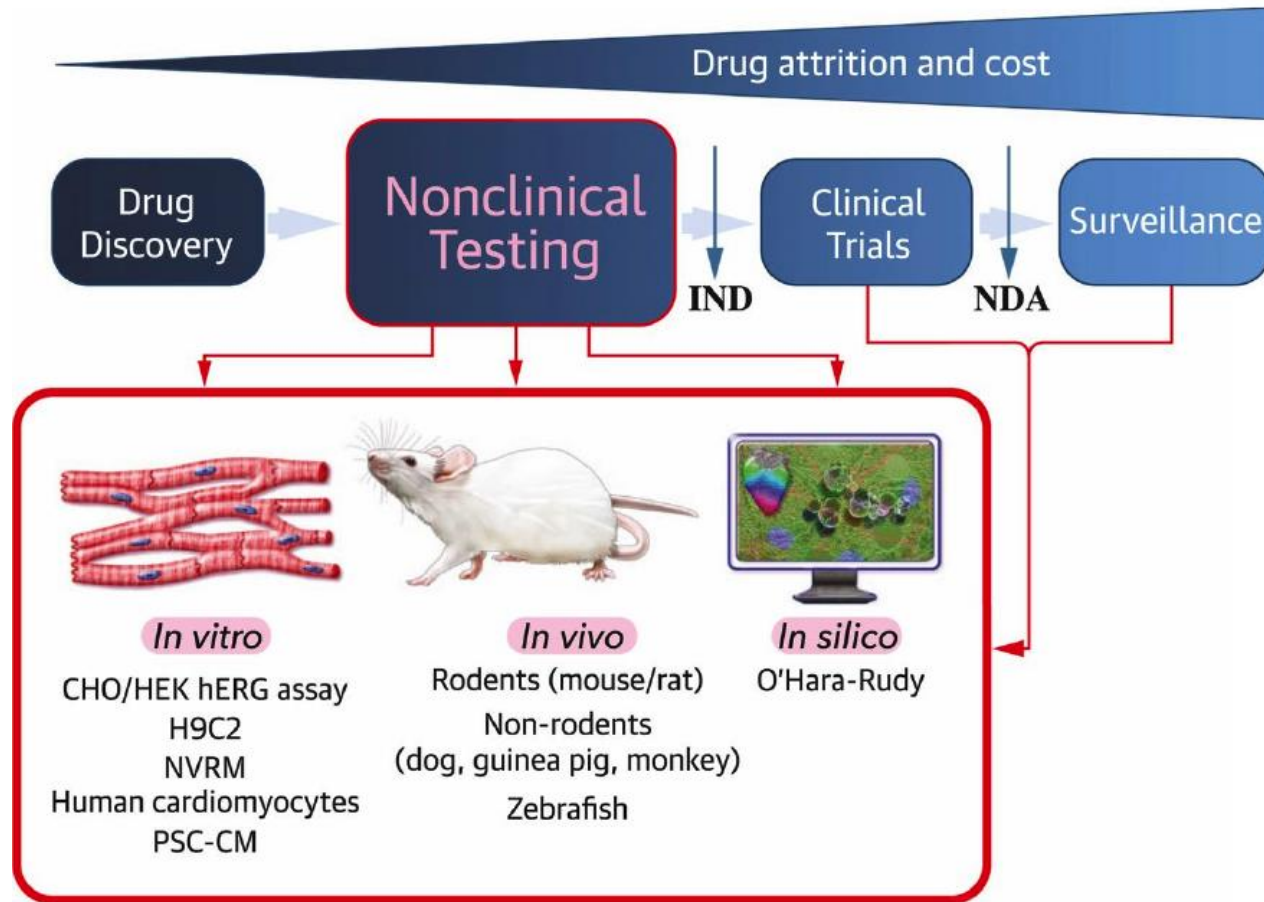


CARDIO-ONCOLOGY

Coordinator: Canan Nebigil



Early detection, signaling,
treatment and prevention of
heart failure induced by cancer
chemotherapeutics



Acknowledgment



cardiovascular



Thank you for your attention!!!