

# From academia to industry, one story of technology transfer

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Stanford University  
School of Medicine

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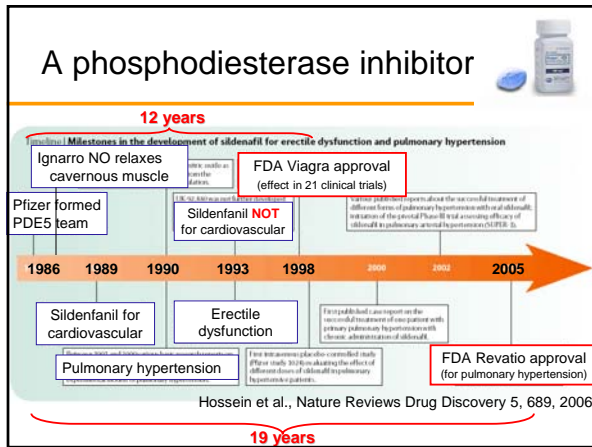
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## A phosphodiesterase inhibitor




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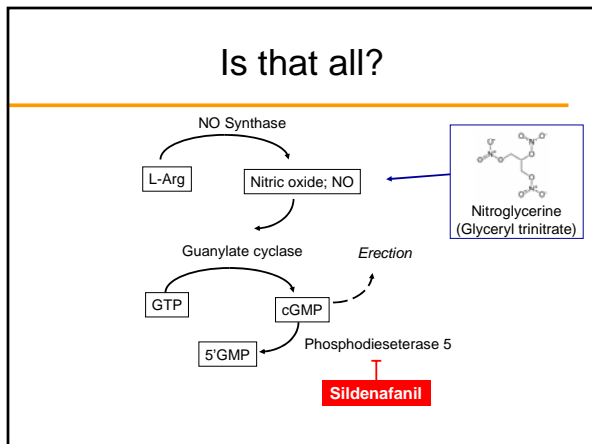
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## Is that all?




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## Did it take that long?

1. Nitroglycerine (NG) **1847** by Sobrero in Turin - 'violent headache'
2. Hering, **1849** - remedy for headache, 'like cures like'.
3. Alfred Nobel (**1851**) overcoming handling problems with detonator. Nobel had angina but did not get NG treatment.
4. **1900**, workers of NG; 'Monday disease', 'Sunday Heart Attacks'
5. Ferid Murad (Stanford) nitric oxide (NO) released from NG and acts on vascular smooth muscle (**1977**).
6. Furchgott and Zawadski acetylcholine-induced vasorelaxation (**1980**)
7. Ignarro and Moncada identified endothelial-derived relaxing factor (EDRF) as NO (**1987**).

Add 140 years to the time line and the scientific effort.

Marsh & Marsh (2000) Clin & Exp Pharm Physiol 27: 313-319

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## From academia to industry, one story of technology transfer

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n=1

no lessons yet

The experiment is on going

### Disclosure:

DMR is the founder, share holder and member of the Board of Directors of KAI Pharmaceuticals

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## The lab's research topic: protein kinase C (PKC) - a family of signaling enzymes

Each PKC isozyme – different role



The question:  
What makes them different?

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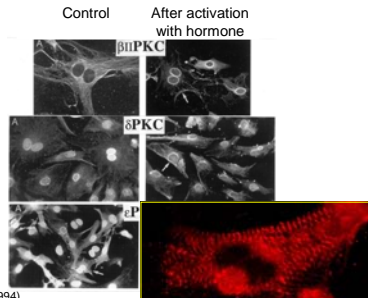
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## Distinct location within the cell; data in heart cells



Laura Cheever (1988)  
Marie-Helene Disatnik (1994)

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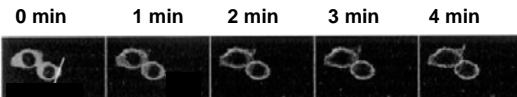
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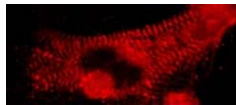
## The challenge – working against the dogma:

Activated PKCs are *all* in the cell periphery,  
where diacylglycerol is found



Over-expressed, GFP-tagged  $\epsilon$ PKC

Endogenous  $\epsilon$ PKC



Debbie Schechtman (2005)

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## Academic research = describe phenomena & provide explanation

### Hypothesis:

Location of each PKC determines its function.

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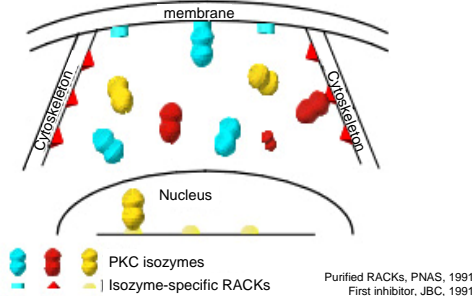
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**Activated PKC isozymes are localized to distinct subcellular sites by anchoring to selective RACKs (Receptors for Activated C-Kinase)**




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**Testing the hypothesis**

**Hypothesis:**

Location of each PKC determines its function.

**Testing the hypothesis:**

**Inhibitors** of location should inhibit the function.

**Activators** of location should induce the function.

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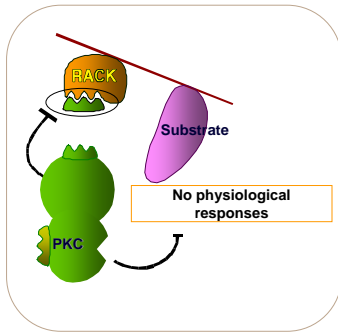
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**Competitive inhibitors of PKC**




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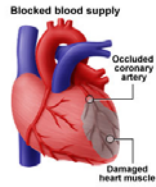
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## How to choose a clinical relevant model/application?



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## $\delta$ PKC inhibitor in models of cardiac ischemia



Chen et al., PNAS 2002

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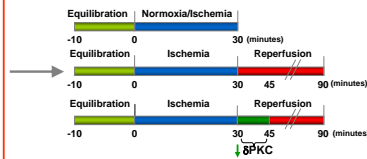
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## Simulated ex vivo ischemia and reperfusion model



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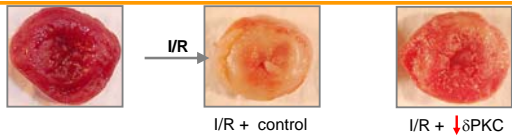
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## Application of $\delta$ PKC inhibitor at reperfusion inhibits cardiac infarction.



$\delta$ PKC inhibitor inhibits I/R-induced

- ↓ Creatine phosphokinase (cytolysis)
- ↑ TTC staining (live tissue)
- ↓ Cell death (necrosis and/or apoptosis)
- ↑ Cardiac function

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## Any clinical use for that?



Fumiaki Ikeno, MD



Koichi Inagaki, MD PhD

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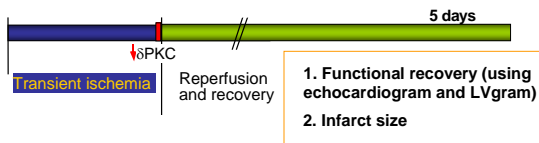
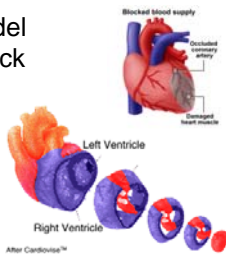
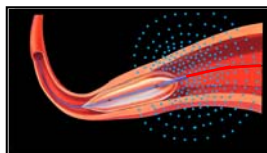
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## Porcine model of heart attack




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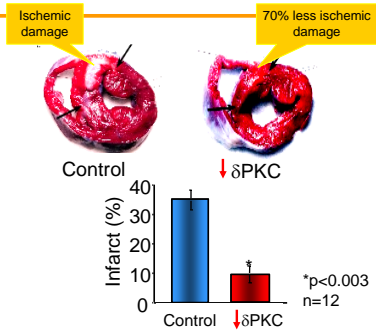
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## δPKC inhibitor reduces infarct size




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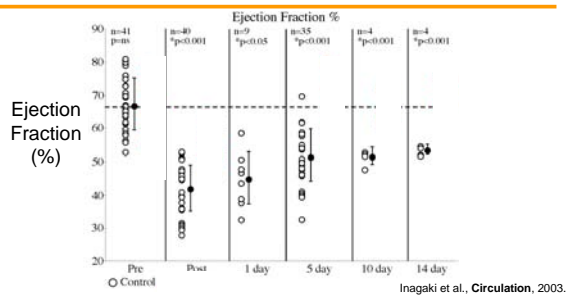
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## δPKC inhibitor delivered at reperfusion improves cardiac function.



δPKC inhibitor confers 100% recovery of cardiac function and myocardial stunning five days after myocardial infarction.

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## δPKC inhibitor reduces reperfusion injury after MI

Treatment with δPKC inhibitor (500ng / Kg) for one minute resulted in:

- 70 percent reduction in infarct size
- Improvement in heart function immediately and is normal by 5 days
- Accelerated ATP regeneration
- Protection from necrosis and apoptosis
- Restoration of microvasculature function and perfusion

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### Can this $\delta$ PKC inhibitor be a drug?

#### What did we have?

- IP: several patents on composition of matter and methods of use (and assays)
- Several publications on cellular basis
- Ongoing studies on molecular basis
- Data in rat, mice and pigs
- Independent corroboration from other labs using the same and different tools

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### How can we *translate* this finding to help patients who have a heart attack?

#### OR what goes into drug development?

- Manufacturing and formulation
  - Toxicity studies
  - Preparation of regulatory documents to the FDA (IND),
  - Safety clinical trials
  - Independent efficacy studies to the FDA (NDA)
  - Preparation of regulatory documents to the FDA (NDA)
- Total cost according to the pharmaceutical industry:  
**\$300-800 million**

This work has to be done outside academia

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### Go talk with Big Pharma

- No to PKC drugs
- No to drug for acute myocardial infarction
- **No No No!**

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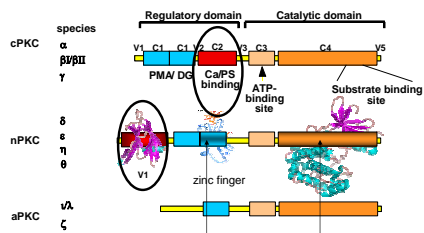
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## PKC family of enzymes are a *challenge* for drug design



20 years of Big pharma efforts did **not** generate isozyme-selective regulators

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## Why not acute myocardial infarction?

Over 30 trials failed already  
 "Reperfusion injury does not exist"  
 "Protein kinase C is spectator (not a player) in cardiac protection" President of international society of heart research  
 A peptide?!  
 That works inside the cell?!  
 Inhibits protein-protein interaction?!

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## Starting KAI Pharmaceuticals

Jan 2002: Talked with ~ 100 clinicians, other entrepreneurs, BD people and anyone who was willing to listen.  
 Focus - getting the drug to patients  
 2002-2003: Operated as a virtual company with one employee  
 2004: Filed IND (worked for a year as CSO)




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IND approved in 2004

$\delta$ PKC Inhibitor:

KAI-9803 for Injection

in Reperfusion Injury

**DELTA·MI**





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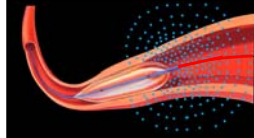
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**KAI-9803 Drug Administration**

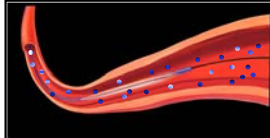

**First injection (balloon catheter)**

- During initial balloon inflation
- 2 mL over 1 minute to infarct area (0.02-2 mg)



**Second injection (guide catheter)**

- 30-50% side branch occlusion by balloon/thrombus
- When TIMI 2/3 flow established
- 3 mL over 1-2 minutes to left coronary system (0.03-3 mg)


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**Starting the clinical trial in Dallas Sept, 2004**



Leon Chen

Kevin Grimes

Activating Dr. Lin's site




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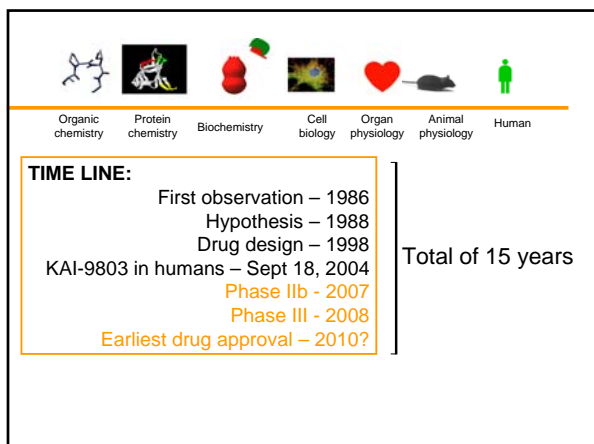
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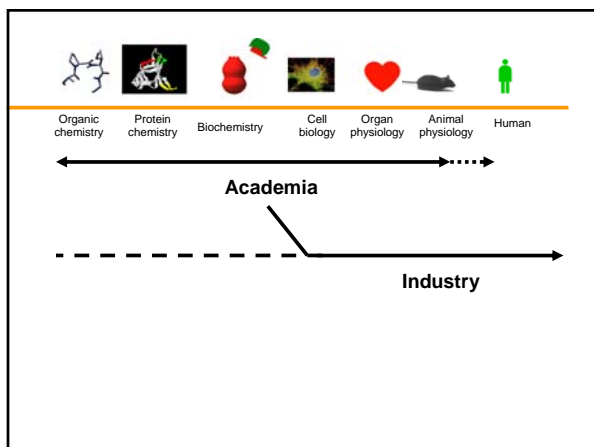
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