From academia to industry, one story of technology transfer

Daria Mochly-Rosen, PhD
Professor, Chemical and Systems Biology
Stanford University
School of Medicine

A phosphodiesterase inhibitor

Is that all?

NO Synthase

\[ \text{L-Arg} \rightarrow \text{Nitric oxide, NO} \]

Nitroglycerine (Glyceryl trinitrate)

Nitric oxide; NO

Guanylate cyclase

Erection

GTP

cGMP

Phosphodiesterease 5

Sildenafil
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).
7. Ignarro and Moncada identified endothelial-derived relaxing factor (EDRF) as NO (1987).

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

From academia to industry, one story of technology transfer

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

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?
Distinct location within the cell; data in heart cells

Control          After activation with hormone

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

The challenge – working against the dogma:
Activated PKCs are all in the cell periphery, where diacylglycerol is found

0 min    1 min    2 min    3 min    4 min
Over-expressed, GFP-tagged εPKC
Endogenous εPKC
Debbie Schechtman (2005)

Academic research = describe phenomena & provide explanation

Hypothesis:
Location of each PKC determines its function.
Activated PKC isozymes are localized to distinct subcellular sites by anchoring to selective RACKs (Receptors for Activated C-Kinase)

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.

Competitive inhibitors of PKC
How to identify short peptides in the 150 aa domain that correspond to protein-protein interactions?

Of the novel PKC isoymes, δ, ε, θ and η, the RACK-binding domain of δPKC (δV1/C2) is most similar to that of θPKC (52% identical).

The least similar sequences between δ and θPKC are likely to mediate interactions with their isozyme-specific RACKs.

δPKC inhibitor as a research tool

Get the peptide into cells:
Digitonin + ATP
Gene transfer (transgenic mice)
Conjugating the peptide to cell permeating TAT-derived peptide (TAT47-57) via Cys S-S bond – easy to use

Demonstrated that δPKC regulates beating rate of heart muscle cells
How to choose a clinical relevant model/application?

δPKC inhibitor in models of cardiac ischemia

Simulated ex vivo ischemia and reperfusion model
Application of δPKC inhibitor at reperfusion inhibits cardiac infarction.

δPKC inhibitor inhibits I/R-induced
- Creatine phosphokinase (cytolysis)
- TTC staining (live tissue)
- Cell death (necrosis and/or apoptosis)
- Cardiac function

Any clinical use for that?

Fumiaki Ikeno, MD
Koichi Inagaki, MD PhD

Porcine model of heart attack

1. Functional recovery (using echocardiogram and LVgram)
2. Infarct size
δPKC inhibitor reduces infarct size

Infarct (%)  
Control  δPKC

70% less ischemic damage

p<0.003  n=12

δPKC inhibitor delivered at reperfusion improves cardiac function.

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

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
Can this δPKC 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

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

Of what goes into drug development?
• Manufacturing and formulation
• Toxicity studies
• Preparing IND or any documents to the FDA (IND),
• Safety clinical trials
• Independent efficacy clinical trial
• Preparation of regulatory documents to the FDA (NDA)
• Total cost according to the pharmaceutical industry:
  $300-800 million

Go talk with Big Pharma
• No to PKC drugs
• No to drug for acute myocardial infarction
• No No No!
PKC family of enzymes are a challenge for drug design

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?!

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)
IND approved in 2004

δPKC Inhibitor:
KAI-9803 for Injection in Reperfusion Injury

**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)

**Starting the clinical trial in Dallas Sept, 2004**
TIME LINE:
First observation – 1986
Hypothesis – 1988
Drug design – 1998
KAI-9803 in humans – Sept 18, 2004
Phase IIb - 2007
Phase III - 2008
Earliest drug approval – 2010?
Total of 15 years

Academia

Industry