How Did I Get Here?  
A Perspective From a Cardiologist in Biotech

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My Scientific Roots

High-resolution tracking of microtubule motility driven by a single kinesin motor

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"Wonderful stuff – but I doubt this will have any use in medicine"
- Fady Malik after handing in his thesis

How lucky can one be? A perspective from a young scientist at the right place at the right time

Ronald D Vale (2012 Lasker Awardee)
Volume 18, Number 10, October 2012, Nature Medicine
10 Lessons for the Young Scientist

1. Find good mentors, learn from them and then develop your own style.
2. Pick an important problem.
3. Get ahead but then take a chance: seek adventure.
4. Read the literature but don’t be crippled by it.
5. You don’t need a fancy lab to do good science.
6. Work hard, play hard and squeeze in time to do your laundry.
7. Persistence is more important than brilliance.
8. No project or career is immune from mistakes.
9. Don’t be afraid to change your life plans.
10. Science is moving fast: hold on and enjoy the ride.
Cytokinetics Corporate History

Pharmaceutical targeting of motor proteins has therapeutic potential!!!

• Commenced operations in 1998 with focus to cytoskeletal biology
• First to develop small molecule inhibitors of mitotic kinesins
• Next focused on the discovery and development of novel small molecule therapeutics that modulate muscle contractility
• Strategic decision in 2008 to focus on a muscle biology portfolio
• Located in South San Francisco, California
• NASDAQ: CYTK (IPO in 2004)
• To date, five drug candidates arising from the company’s research activities have been progressed into clinical development
• Corporate strategy:
  • Fully-integrated biopharmaceutical company
  • First-in-class novel mechanism compounds

Rule #3: Get ahead but then take a chance: seek adventure.
Rule #9: Don’t be afraid to change your life plans.
Small Molecules Can Improve Cardiac Function…

**Indirect Mechanisms**

PKA phosphorylates proteins throughout the myocyte

Intracellular [Ca^{2+}] increases

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PKA phosphorylates proteins throughout the myocyte

Intracellular [Ca^{2+}] increases

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**Diagram:**

- PKA
- Adenylyl Cyclase
- Ca^{2+} Channel (L-type)
- K^{+} Channel
- AD or MUSC Receptor
- βAR
- Giα
- Gsα
- βγ

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**Metabolic Enzymes:**

- ATPase
- Phospholamban
- Phospholamban-P

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**Ca^{2+} Release Channel:**

- SR

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**Cardiac Sarcomere:**
... But They Compromise Cardiac Performance

**Indirect Mechanisms**

PKA phosphorylates proteins throughout the myocyte

- Intracellular [Ca\(^{2+}\)] increases
- Contractility
- Heart rate
- Blood Pressure
- O\(_2\) Demand
- Efficiency
- Arrhythmias

Dobutamine (β-agonist), Milrinone (PDE3\(_i\))
Potential Advantages of Targeting the Sarcomere

**Therapeutic Hypothesis**

Directly target the sarcomere

Ø PKA activation

Intracellular [Ca^{2+}] unchanged

Contractility

Heart rate?

Blood Pressure?

O_{2} Demand?

Efficiency?

Arrhythmias?

Effective Drug?
Why Focus on Cardiac Function?

Systolic dysfunction is at the “heart” of the matter

Cardiac Contractility

Renin-Angiotensin System
Sympathetic Nervous System

Rule #2: Pick an important problem.
Rule #4: Read the literature but don’t be crippled by it.
Why Focus on Cardiac Function?

• Improving cardiac function works (at least for devices)!
  – Cardiac Resynchronization Therapy
The Sarcomere
The Basic Contractile Unit of Muscle
The Sarcomere Can Be Reconstituted
*In Vitro Motility Assay*

Fluorescent Actin/Thin Filaments

Myosin Coated Glass Surface

*Myosin*

*Kinesin*
Vale, et al, Cell 1985

2012 Lasker Awardees
High Throughput Screening of a Functional Sarcomere
Lead Optimization is Complex!

- **Compound Design and Synthesis**
- **Assess In Vitro Activity**
  - Functional Cardiac Sarcomere
  - Cardiac Myocyte Profiling
- **Assess Drug-Like Properties**
  - Drug Metabolism and Pharmacokinetics
  - Solubility
- **Rule out Undesired Activities**
  - Alteration of Ca2+ Transient
  - PDE III Inhibition
- **Demonstrate In Vivo Activity**
  - Rat Efficacy Model
  - Instrumented Dog Model of Heart Failure
  - Preclinical evaluation

Drug Candidate
Key Milestones Leading to Drug Candidate

CK-0156636

1

CK-1032100

2

CK-1213296

3

CK-1122534

4

CK-1317138

5

Omeprazol Mecarbil (CK-1827452)

>1700 Compounds Synthesized and Tested
How Does a Cardiac Myosin Activator Work?

The Chemical and Mechanical Cycles are Linked

**The Actin–Myosin Cycle**

- **Weak Binding**
  - ADP–P_i
  - ATP
  - ADP–Pi
  - Pi

- **Strong Binding**
  - ATP
  - ADP

*Force-production*

- Myosin
- Actin

*Omecamtiv mecarbil* increases the transition rate from weak to strong binding states

**Graph:**

- **Y-axis:** k_{obs} (s^{-1})
- **X-axis:** Omecamtiv mecarbil (mol/L)

Malik et al., 2011

*Omecamtiv mecarbil* increases the number of independent force generators (myosin heads) interacting with the actin filament

“More hands pulling on the rope”
Omecamtiv Mecarbil
A Cardiac Myosin Activator

• Key Characteristics
  – Selective activator of cardiac myosin
  – Prolongs duration of systole by
    o Increasing entry rate of myosin into force-producing state
    o Thus increasing overall number of active cross-bridges
  – No increase in myocyte calcium
  – Increases stroke volume
  – No change in $dP/dt_{max}$
  – No increase in MVO$_2$

Omecamitv Mecarbil
(MW = 401.43)

Vale and Milligan, Science 2000
Omecamtiv Mecarbil: Dog Heart Failure Model

Increases Duration but not Velocity of Contraction

Time-dependent Elastance \([E(t)]\)

MVO\(_2\) Increased

MVO\(_2\) Unchanged

Malik et al, 2011
Clinical Experience with a Selective Cardiac Myosin Activator
(Omecamtv Mecarbil)
CY 1111
Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous CK-1827452 in Healthy Volunteers

Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study

John R Teerlink, Cyril P Clarke, Khalil G Saikali, Jacqueline H Lee, Michael M Chen, Rafael D Escandon, Lyndsey Elliott, Rachel Bee, Mohammad Reza Habibzadeh, Jonathan H Goldman, Nelson B Schiller, Fady I Malik, Andrew A Wolff

Lancet 2011; 378: 667–75
Increases in Systolic Ejection Time Underlie Increases in Cardiac Function

Δ = placebo corrected change from baseline
Mean ± SEM
CY 1121
Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous CK-1827452 in Patients with Stable Heart Failure

The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial


Lancet 2011; 378: 676–83
Increases in Systolic Ejection Time...

SET vs. [Omecamtiv Mecarbil] (ng/mL)
Cohorts 1, 2, 3, 4, and 5 at times 1.5 and 24 hours

SET (msec)

Change from Baseline

[Omecamtiv mecarbil] (ng/mL)
24 hour infusion
Peak [omecamtiv mecarbil] = 378 ng/mL

<table>
<thead>
<tr>
<th></th>
<th>SET (msec)</th>
<th>LVOT SV (mL)</th>
<th>EF (%)</th>
<th>HR (bpm) – supine ECG</th>
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<tr>
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<td></td>
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The Systolic Ejection Time PK/PD Response is the Same in HF Patients and Healthy Volunteers
Targeting Muscle Contractility

*Diversity of Contractile Function*

**Cardiac Muscle**
- Ventricular ejection
- Ventricular filling

**Skeletal Muscle**
- Strength
- Mobility

**Smooth Muscle**
- Bronchial tone
- Pulmonary vascular tone
- Systemic vascular tone
Targeting Muscle Contractility

Diversity of Therapeutic Application

Cardiac Muscle
- Systolic heart failure
- Diastolic heart failure

Skeletal Muscle
- Neuromuscular dysfunction
- Muscle weakness/wasting

Smooth Muscle
- Asthma/COPD
- Pulmonary hypertension
- Systemic hypertension

Rule #7: Persistence is more important than brilliance!
Rule #10: Science is moving fast: hold on and enjoy the ride.
In Conclusion

While science is a combination of skill and luck...

In the fields of observation, chance favors only the prepared mind.

- Louis Pasteur,
  Lecture, University of Lille (7 December 1854)
Acknowledgements

• Too numerous to count…
  – A large group of people at Cytokine and Amgen
  – Academic Collaborators
  – Clinical Investigators
  – Healthy Volunteers
  – and of course the Patients for whom the therapy is intended

Rule #1: Find good mentors, learn from them and then develop your own style.