

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

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Research & Early Development
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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.

Potential Advantages of Targeting the Sarcomere

Therapeutic Hypothesis

Directly target the sarcomere

∅ PKA activation

Intracellular $[Ca^{2+}]$ unchanged

↑ Contractility

↔ Heart rate?

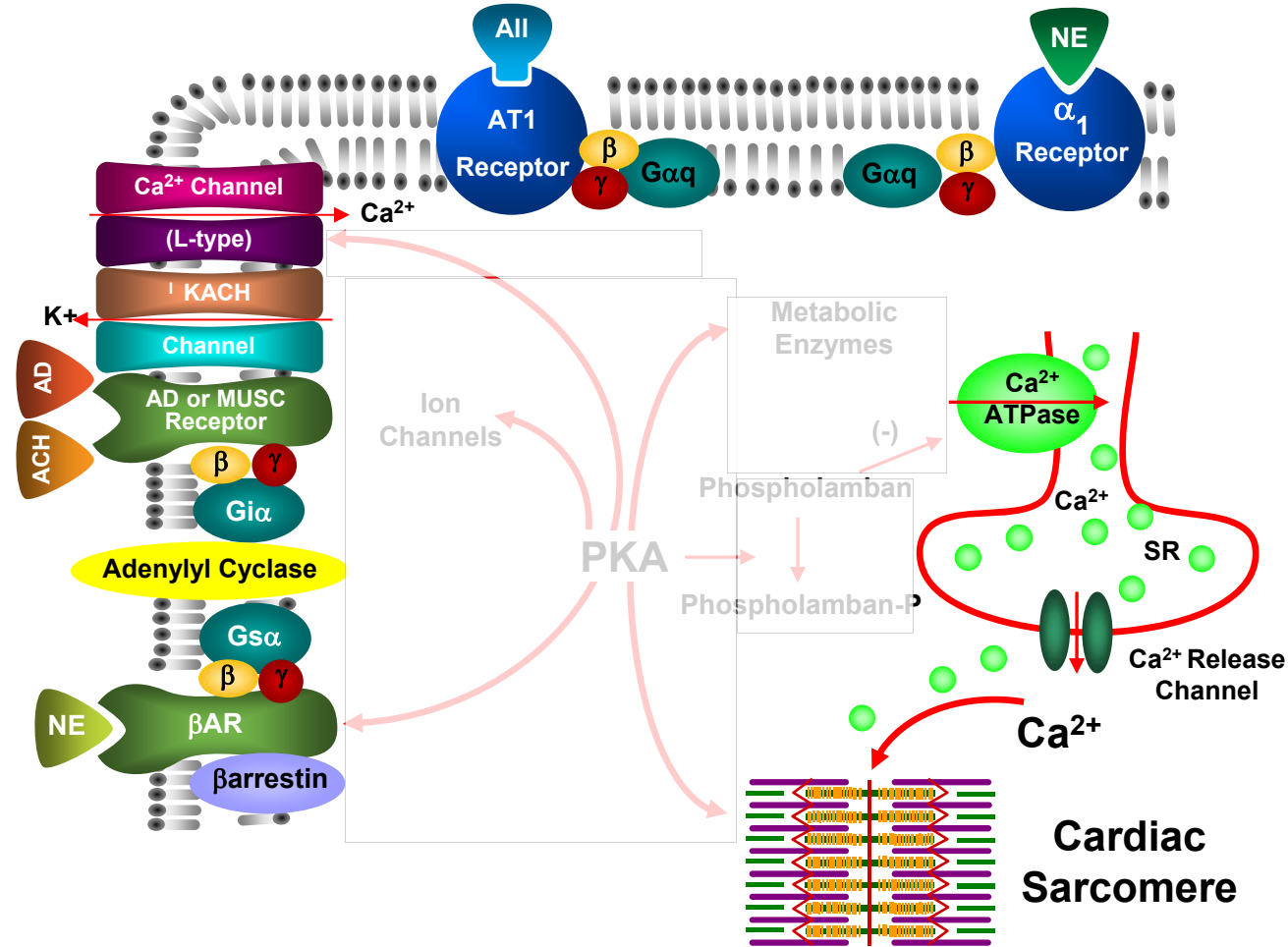
↔ Blood Pressure?

↔ O_2 Demand?

↑ Efficiency?

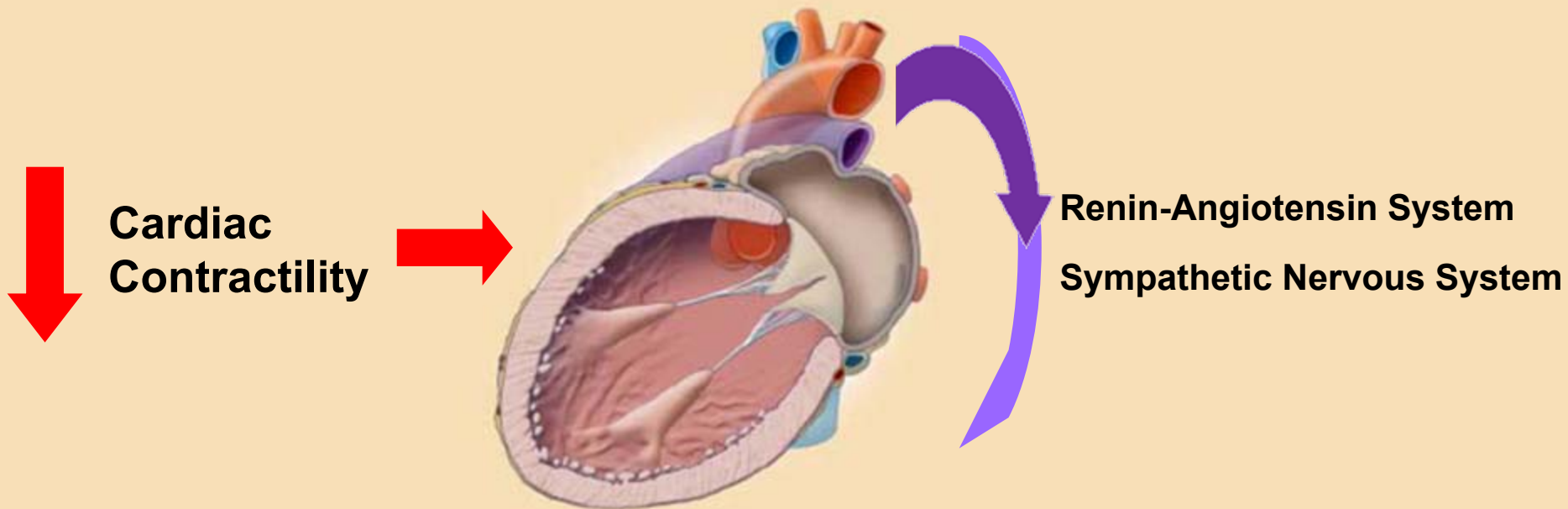
↔ Arrhythmias?

Effective Drug?



Why Focus on Cardiac Function?

Systolic dysfunction is at the “heart” of the matter



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 **NEW ENGLAND**
JOURNAL of MEDICINE

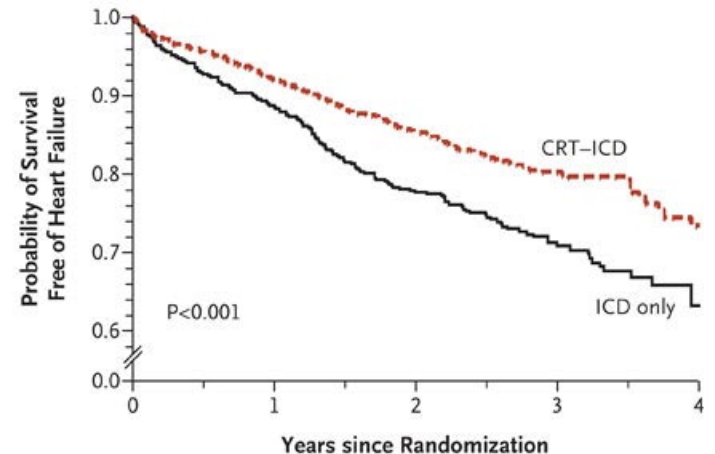
ESTABLISHED IN 1812

OCTOBER 1, 2009

VOL. 361 NO. 14

Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events

Arthur J. Moss, M.D., W. Jackson Hall, Ph.D., David S. Cannom, M.D., Helmut Klein, M.D., Mary W. Brown, M.S., James P. Daubert, M.D., N.A. Mark Estes III, M.D., Elyse Foster, M.D., Henry Greenberg, M.D., Steven L. Higgins, M.D., Marc A. Pfeffer, M.D., Ph.D., Scott D. Solomon, M.D., David Wilber, M.D., and Wojciech Zareba, M.D., Ph.D., for the MADIT-CRT Trial Investigators*



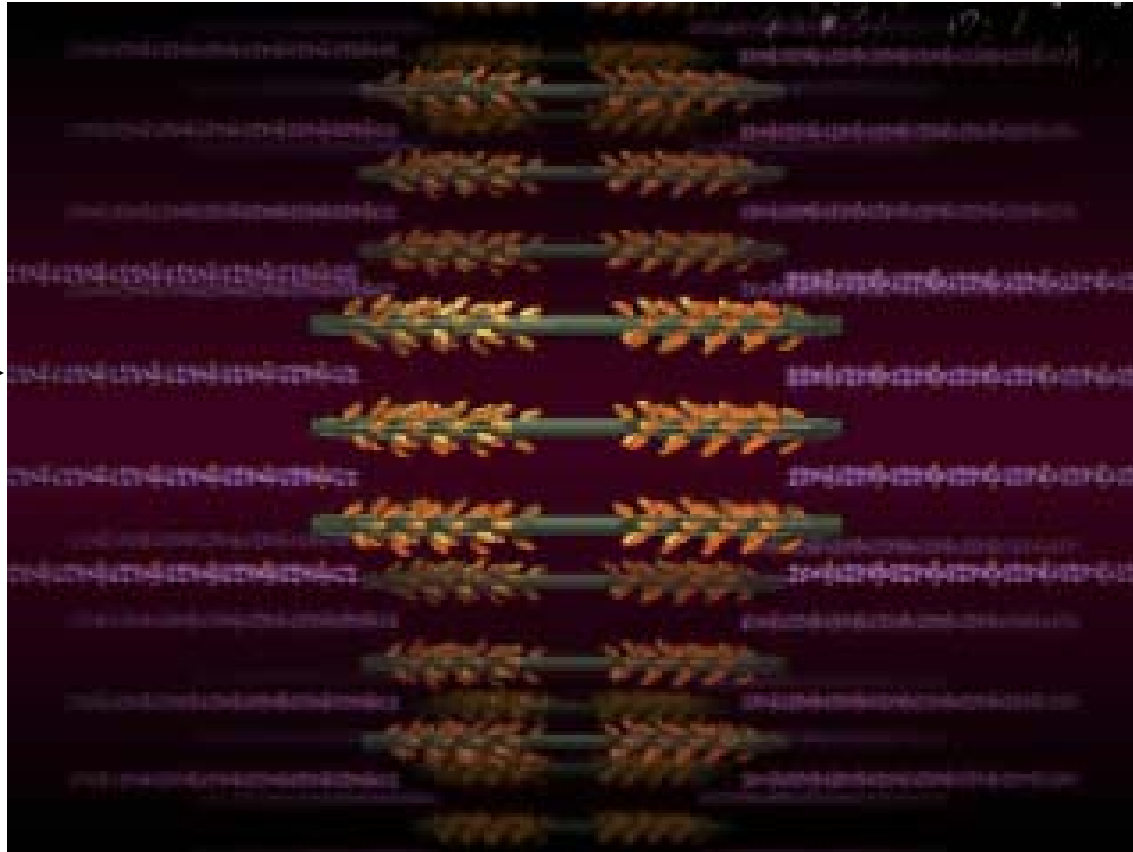
No. at Risk (Probability of Survival)

	0	1	2	3	4
ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT-ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

The Sarcomere

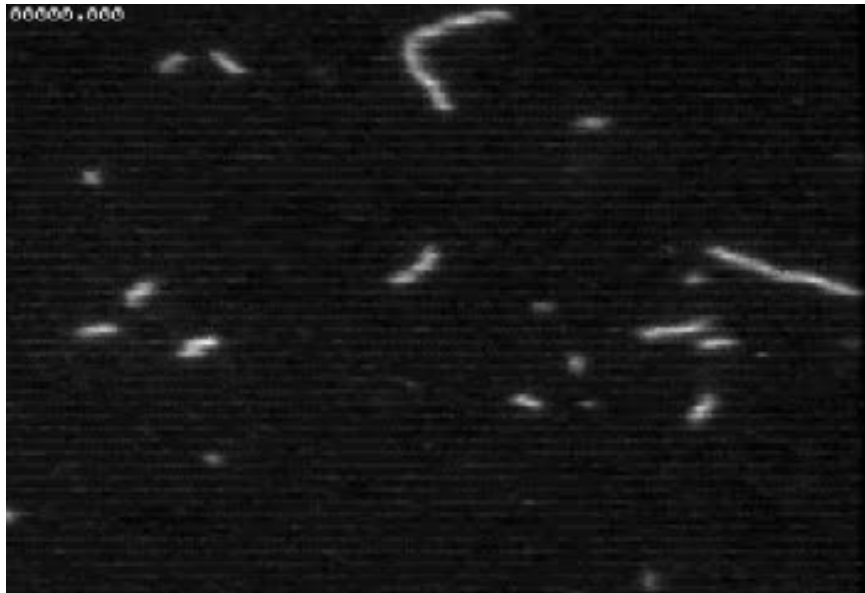
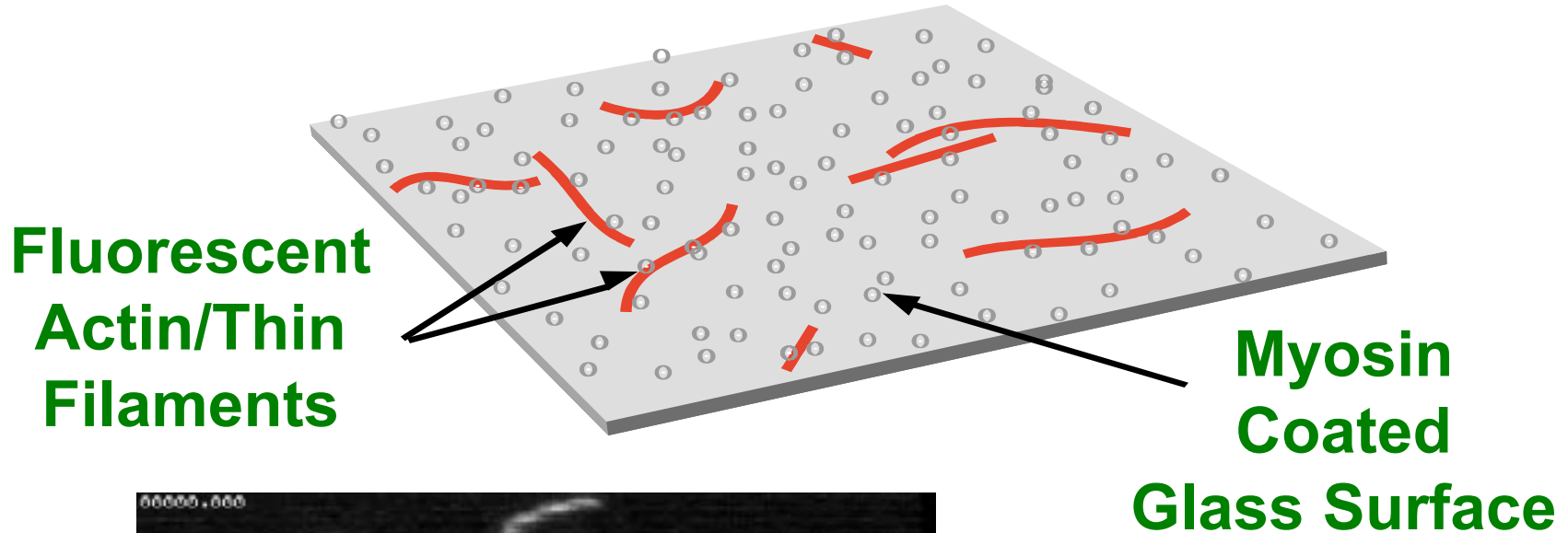
The Basic Contractile Unit of Muscle

Thin
Filament →



← Thick
Filament

The Sarcomere Can Be Reconstituted *In Vitro* Motility Assay



Myosin

Spudich, et al, *Nature* 1985

Toyoshima, et al, *Nature* 1987

Kinesin

Vale, et al, *Cell* 1985

2012 Lasker Awardees

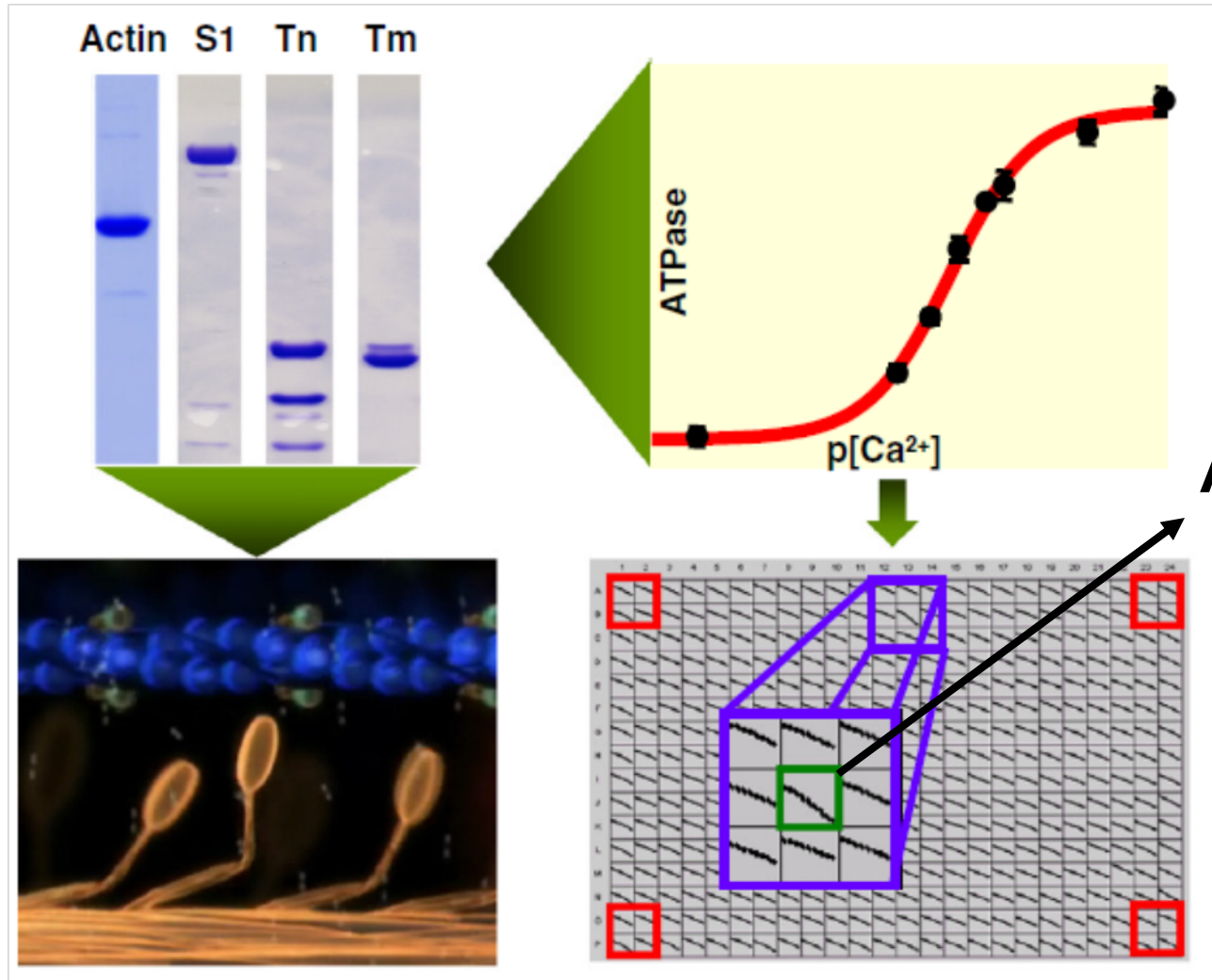


AMGEN

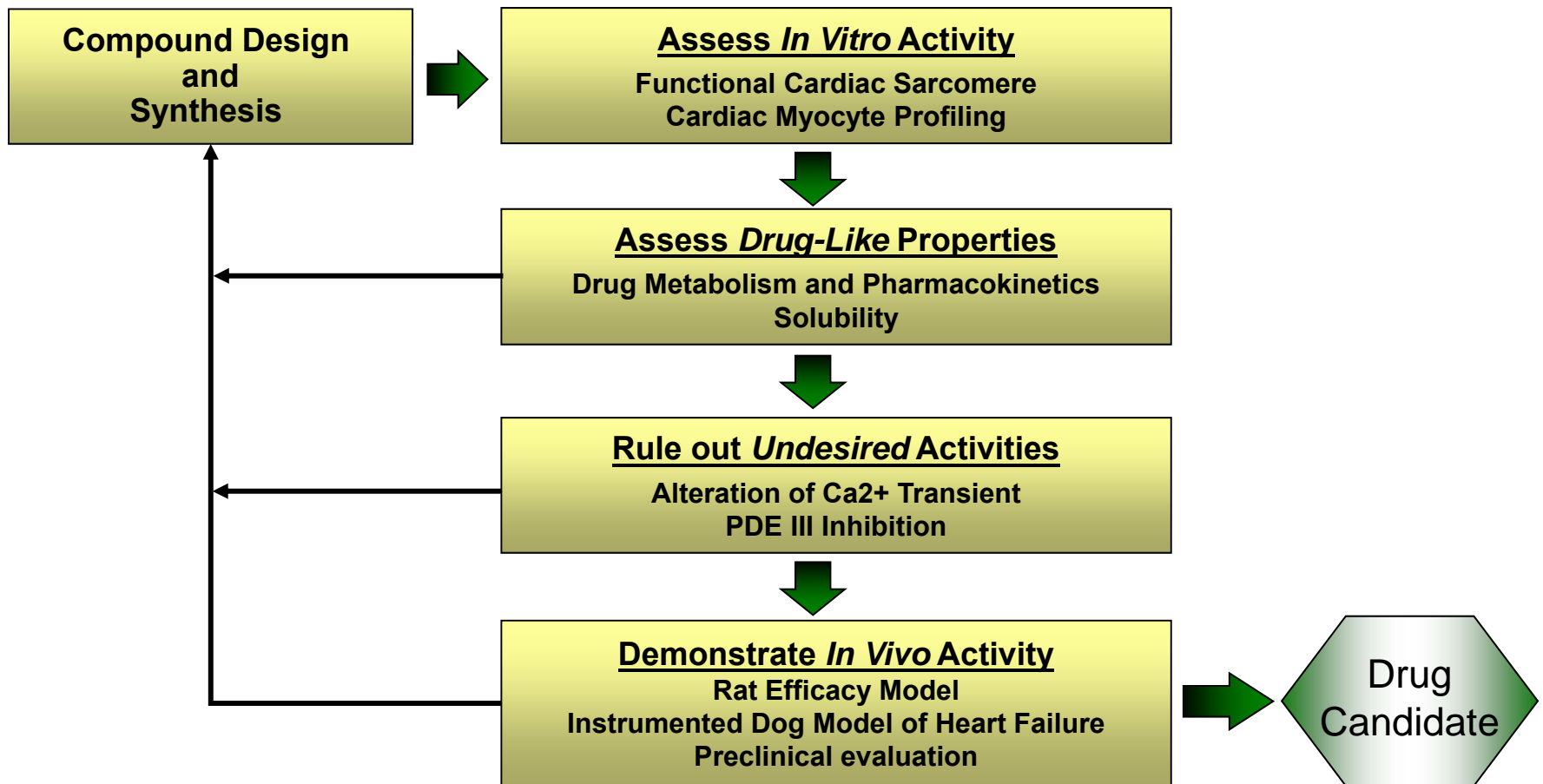


CYTOKINETICS

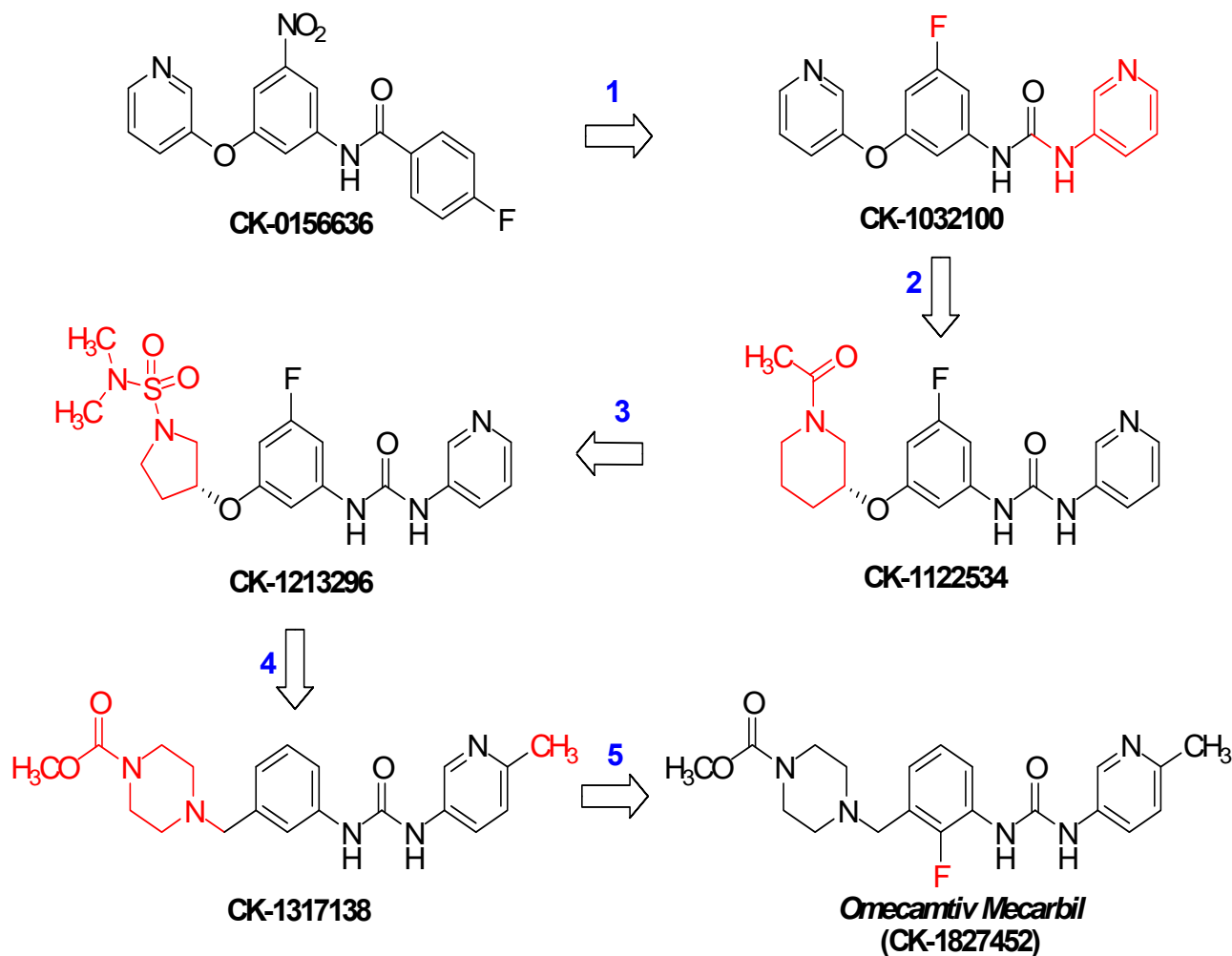
High Throughput Screening of a Functional Sarcomere



Lead Optimization is Complex!



Key Milestones Leading to Drug Candidate

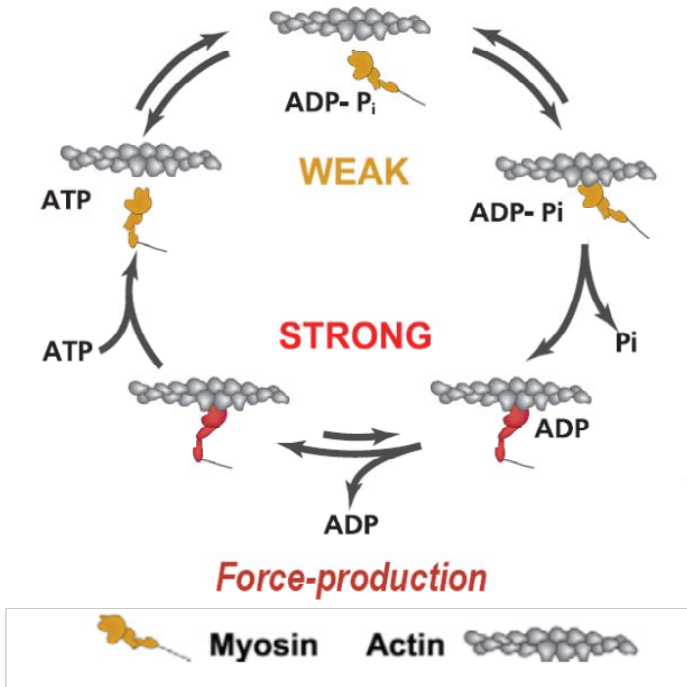


>1700 Compounds Synthesized and Tested

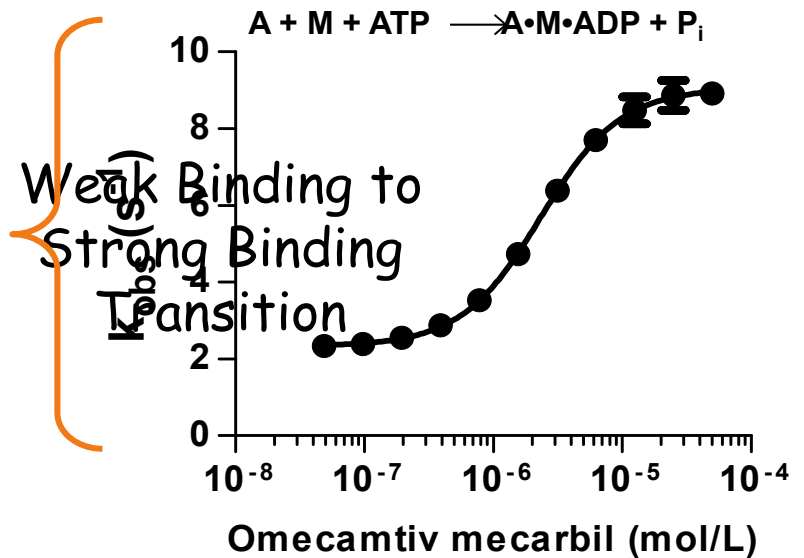
How Does a Cardiac Myosin Activator Work?

The Chemical and Mechanical Cycles are Linked

The Actin-Myosin Cycle



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



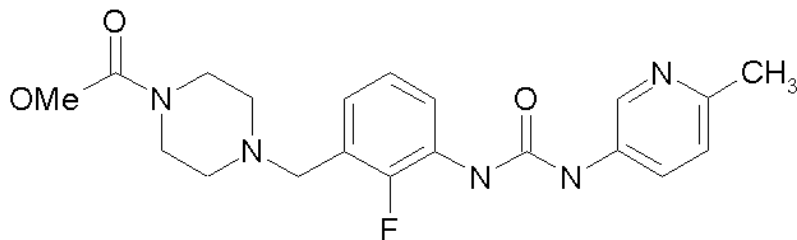
Omecamtiv mecarbil increases the number of independent force generators (myosin heads) interacting with the actin filament
 "More hands pulling on the rope"

Omecamtiv Mecarbil

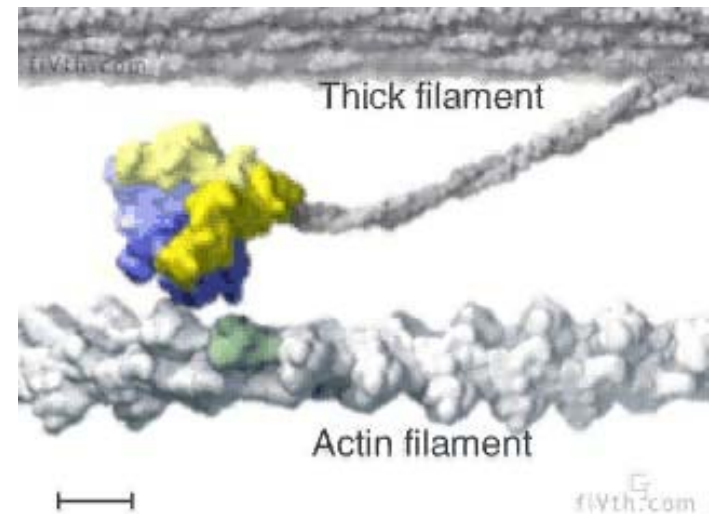
A Cardiac Myosin Activator

- Key Characteristics

- Selective activator of cardiac myosin
- Prolongs duration of systole by
 - Increasing entry rate of myosin into force-producing state
 - 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



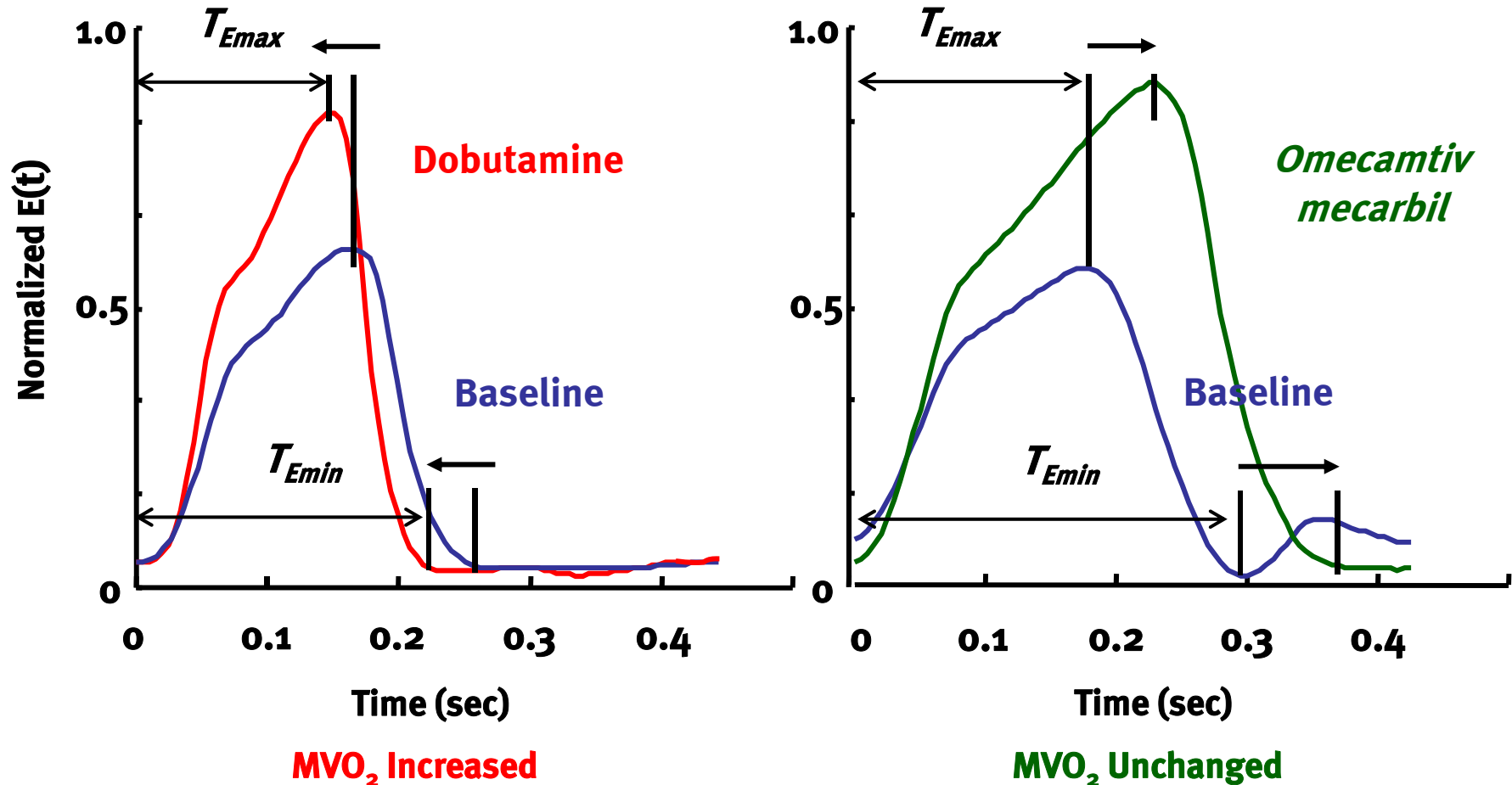
Omecamtiv Mecarbil
(MW = 401.43)



Vale and Milligan, Science 2000

Omecamtiv Mecarbil: Dog Heart Failure Model *Increases Duration but not Velocity of Contraction*

Time-dependent Elastance [E(t)]



Clinical Experience with a Selective Cardiac Myosin Activator (Omecamtiv Mecarbil)

CY 1111

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous CK-1827452 in Healthy Volunteers

THE LANCET

"Management of heart failure can only grow as a concern for patients, doctors, and health-system architects worldwide."



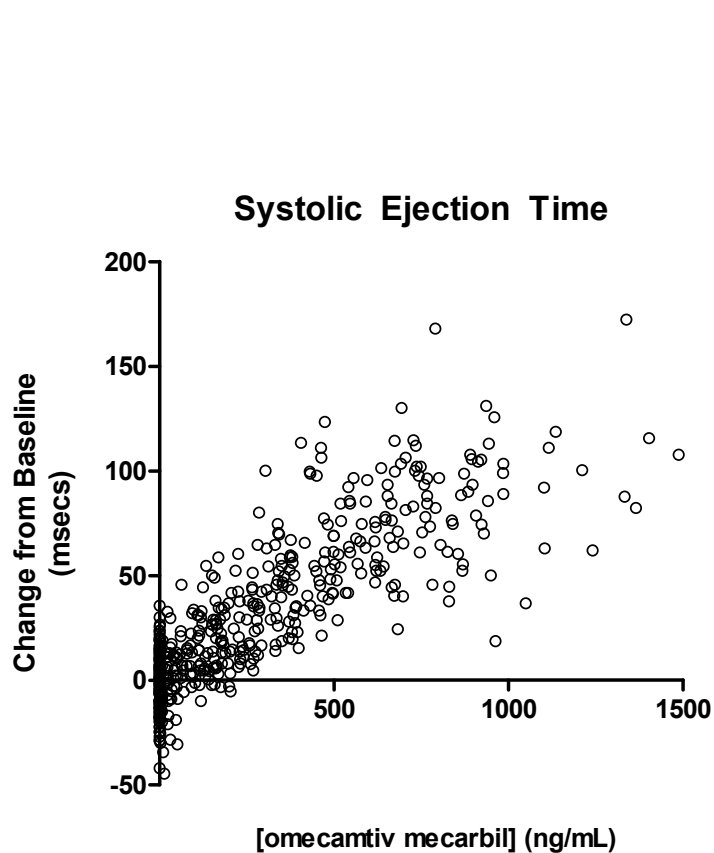
Management of heart failure can only grow as a concern for patients, doctors, and health-system architects worldwide	667
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Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study

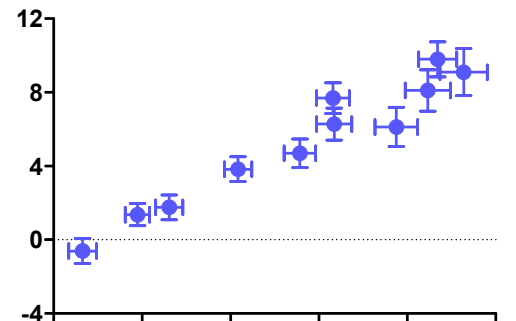
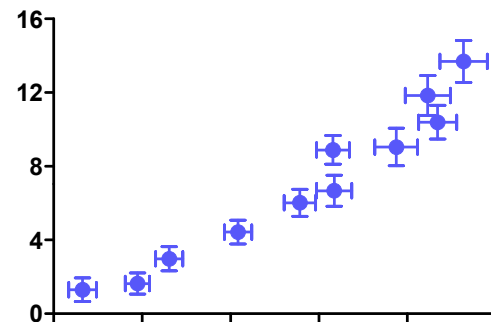
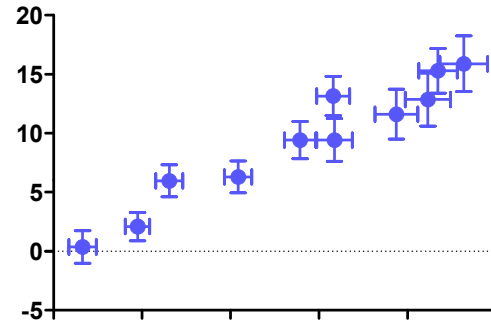
John R Teerlink, Cyril P Clarke, Khalil G Saikali, Jacqueline H Lee, Michael M Chen, Rafael D Escandon, Lyndsey Elliott, Rachel Bee, Mohammad Reza Habibzadeh, Jonathan H Goldman, Nelson B Schiller, Fady I Malik, Andrew A Wolff

Lancet 2011; 378: 667–75

Increases in Systolic Ejection Time Underlie Increases in Cardiac Function



Δ = placebo corrected change from baseline
Mean \pm SEM



2 Δ SET (msec)



CY 1121

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous CK-1827452 in Patients with Stable Heart Failure

THE LANCET

"Management of heart failure can only grow as a concern for patients, doctors, and health-system architects worldwide."

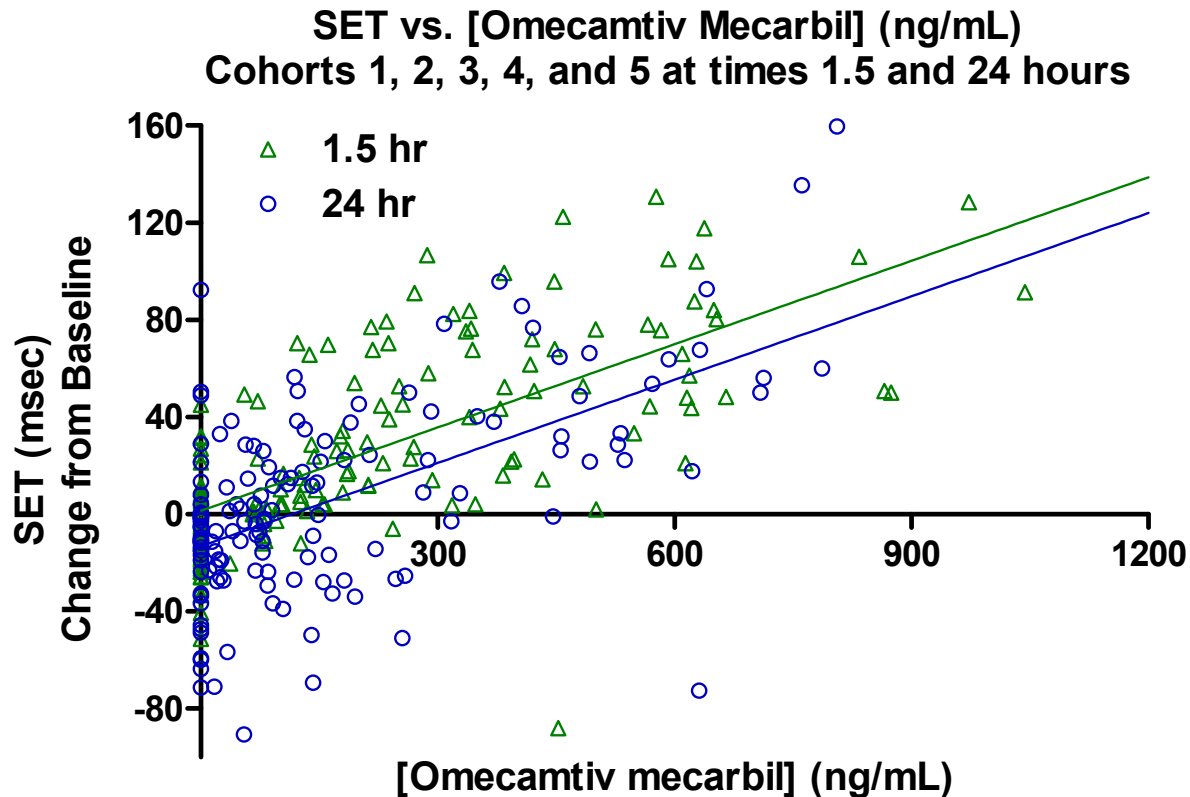


The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial

John G F Cleland, John R Teerlink, Roxy Senior, Evgeny M Nifontov, John J V Mc Murray, Chim C Lang, Vitaly A Tsyrlin, Barry H Greenberg, Jamil Mayet, Darrel P Francis, Tamaz Shaburishvili, Mark Monaghan, Mitchell Saltzberg, Ludwig Neyses, Scott M Wasserman, Jacqueline H Lee, Khalil G Saikali, Cyril P Clarke, Jonathan H Goldman, Andrew A Wolff, Fady I Malik

Lancet 2011; 378: 676–83

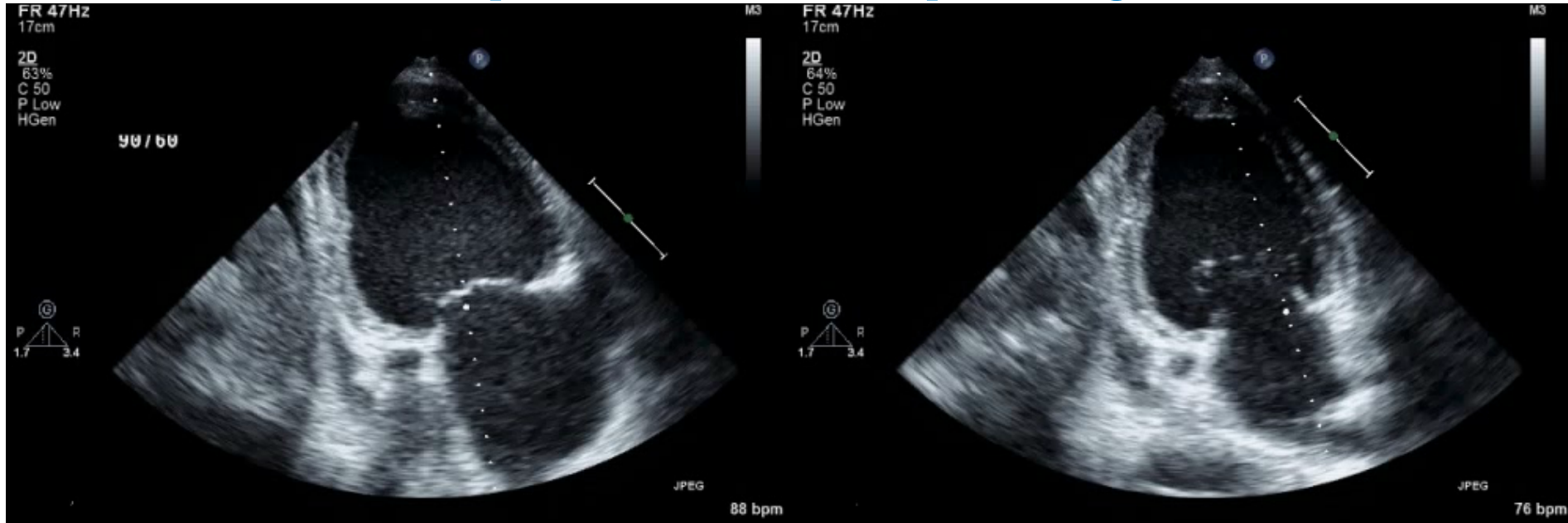
Increases in Systolic Ejection Time...



CY 1121: Effect of Omecamtiv Mecarbil in a Subject with Stable Heart Failure

24 hour infusion

Peak [omecamtiv mecarbil] = 378 ng/mL



Baseline

24 hours

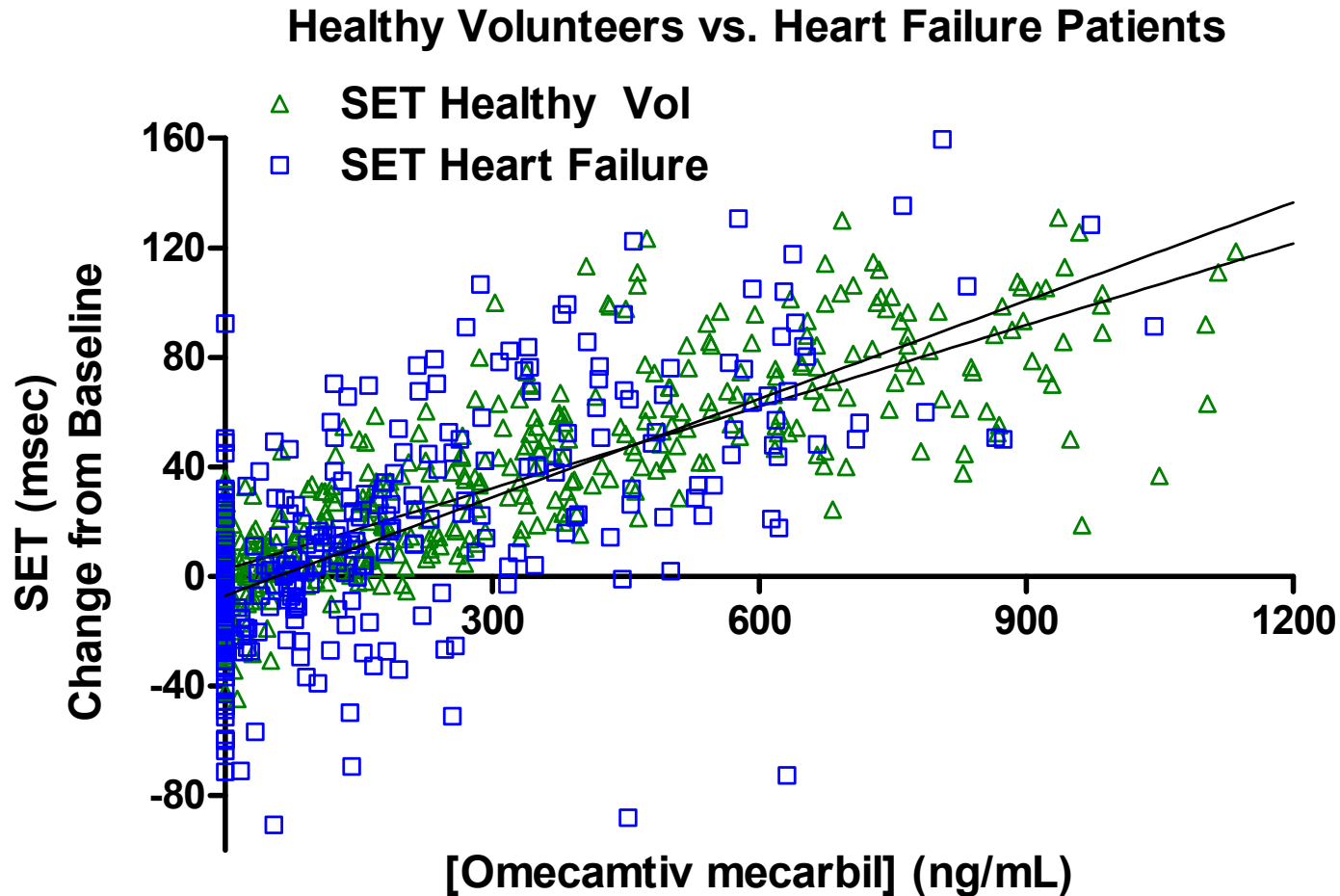
	SET (msec)		LVOT SV (mL)		EF (%)		HR (bpm) – supine ECG	
	Baseline	24 hrs	Baseline	24 hrs	Baseline	24 hrs	Baseline	24 hrs
Omecamtiv mecarbil	216	311	23	54	18	23	88	57
Placebo	234	225	26	24	18	18	85	86

AMGEN



CYTOKINETICS

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

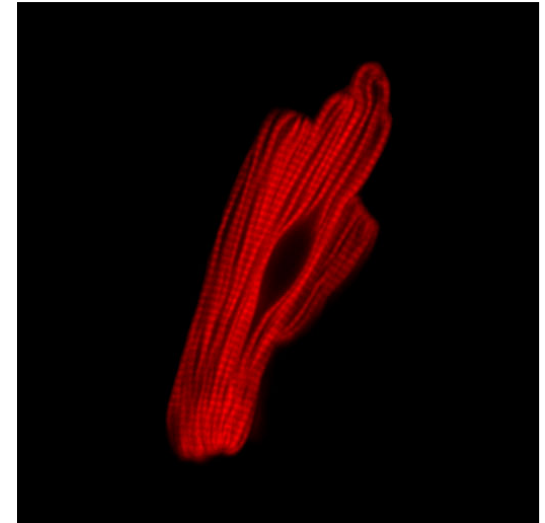
- Ventricular ejection
- Ventricular filling

Skeletal Muscle

- Strength
- Mobility

Smooth Muscle

- Bronchial tone
- Pulmonary vascular tone
- Systemic vascular tone



Targeting Muscle Contractility

Diversity of Therapeutic Application

Cardiac Muscle

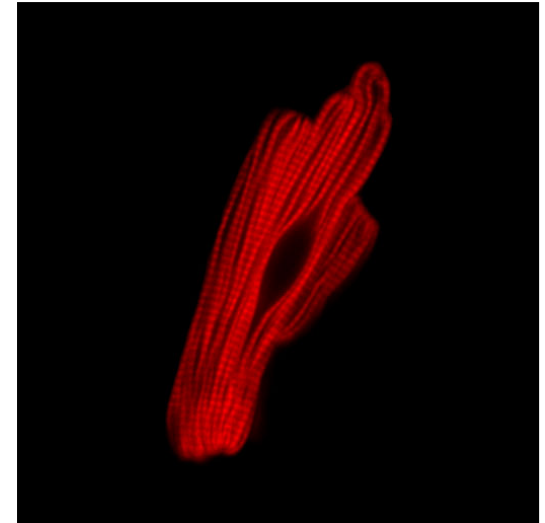
- Systolic heart failure
- Diastolic heart failure

Skeletal Muscle

- Neuromuscular dysfunction
- Muscle weakness/wasting

**nature
medicine**

Russell et al, 2012



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 Cytokinetics 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.