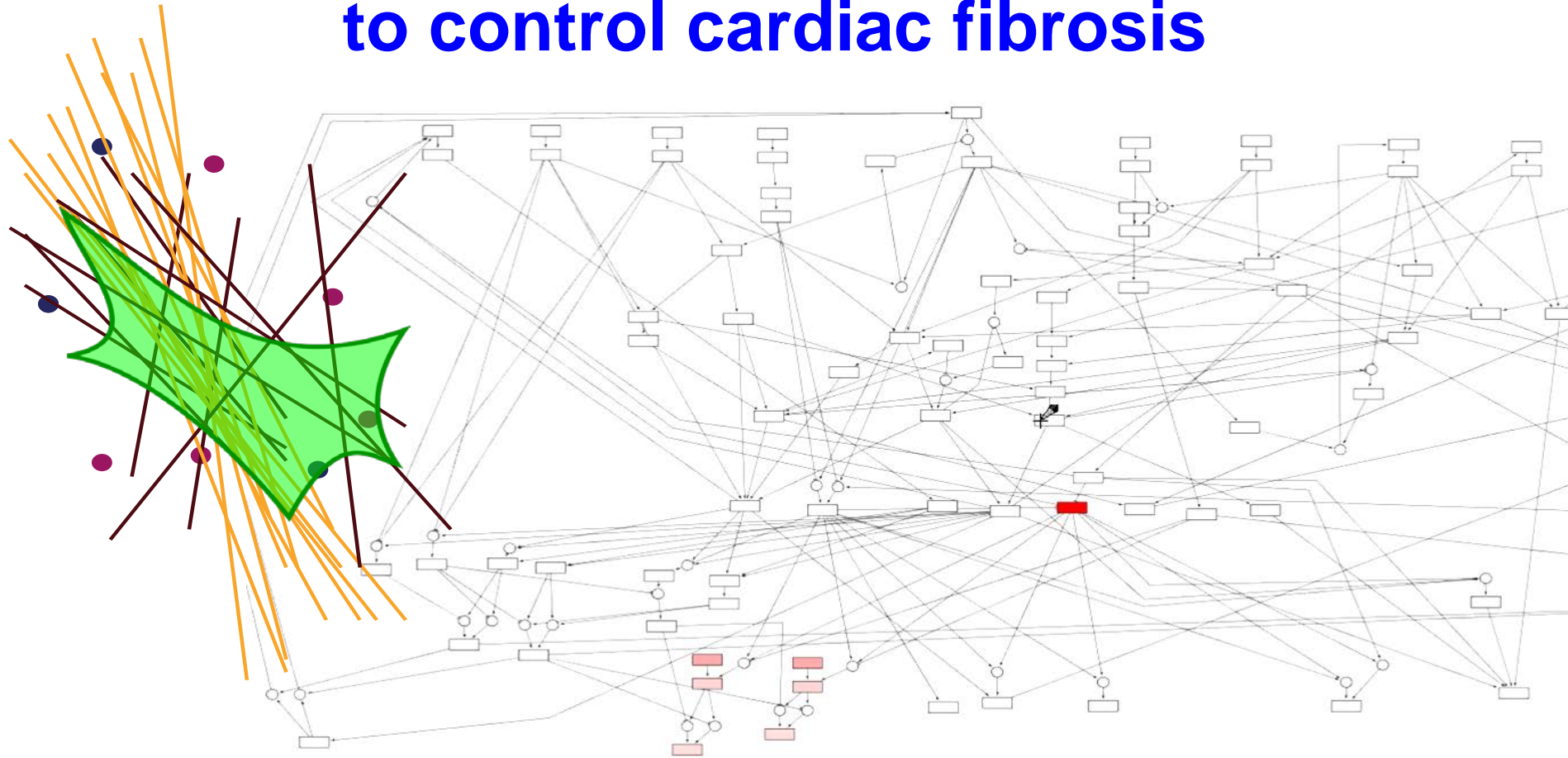


# Systems pharmacology model to control cardiac fibrosis



**Jeff Saucerman**

IMAG MSM March 2019



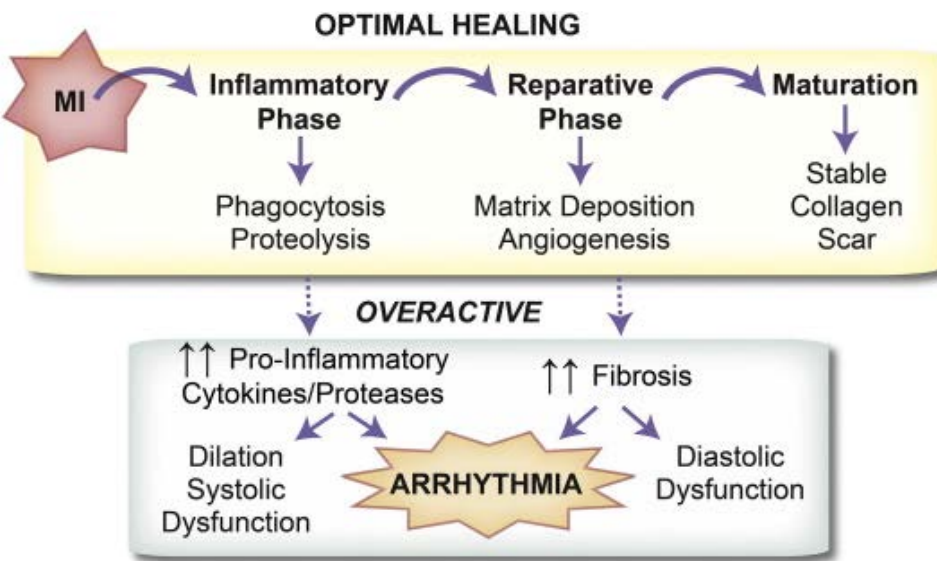
UNIVERSITY  
of VIRGINIA

BIOMEDICAL ENGINEERING

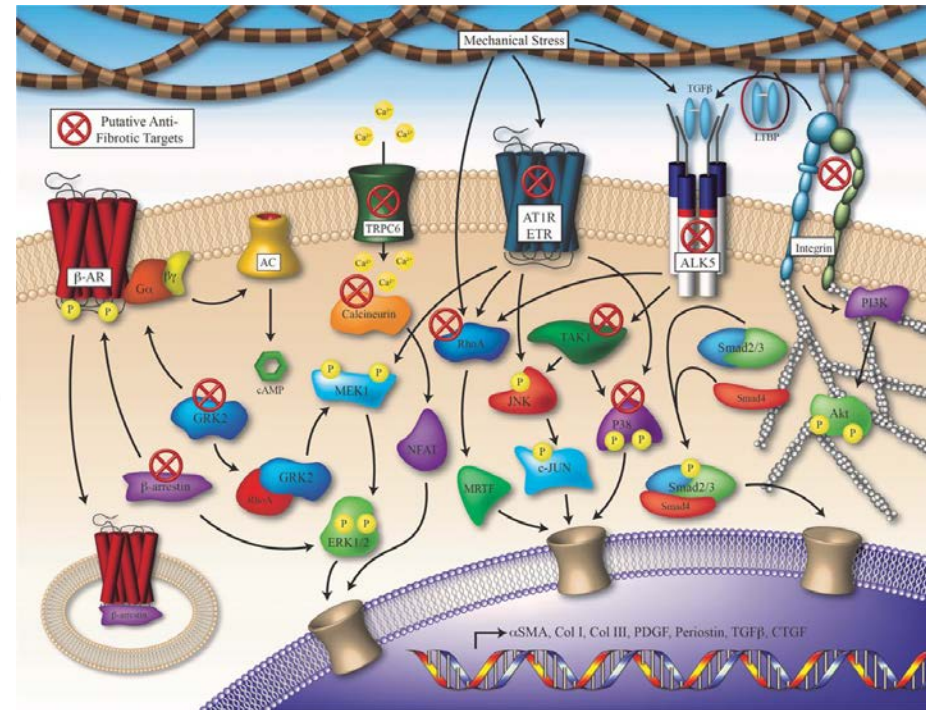


# Signaling complexity hinders targeting of fibrosis after myocardial infarction

Every year, ~1M Americans have a myocardial infarction



Stuart et al JMCC 2016



Travers et al Circ Res 2016

**Objective:** Develop computational models that predict and mechanistically explain therapeutic strategies to control myofibroblast activation and fibrosis

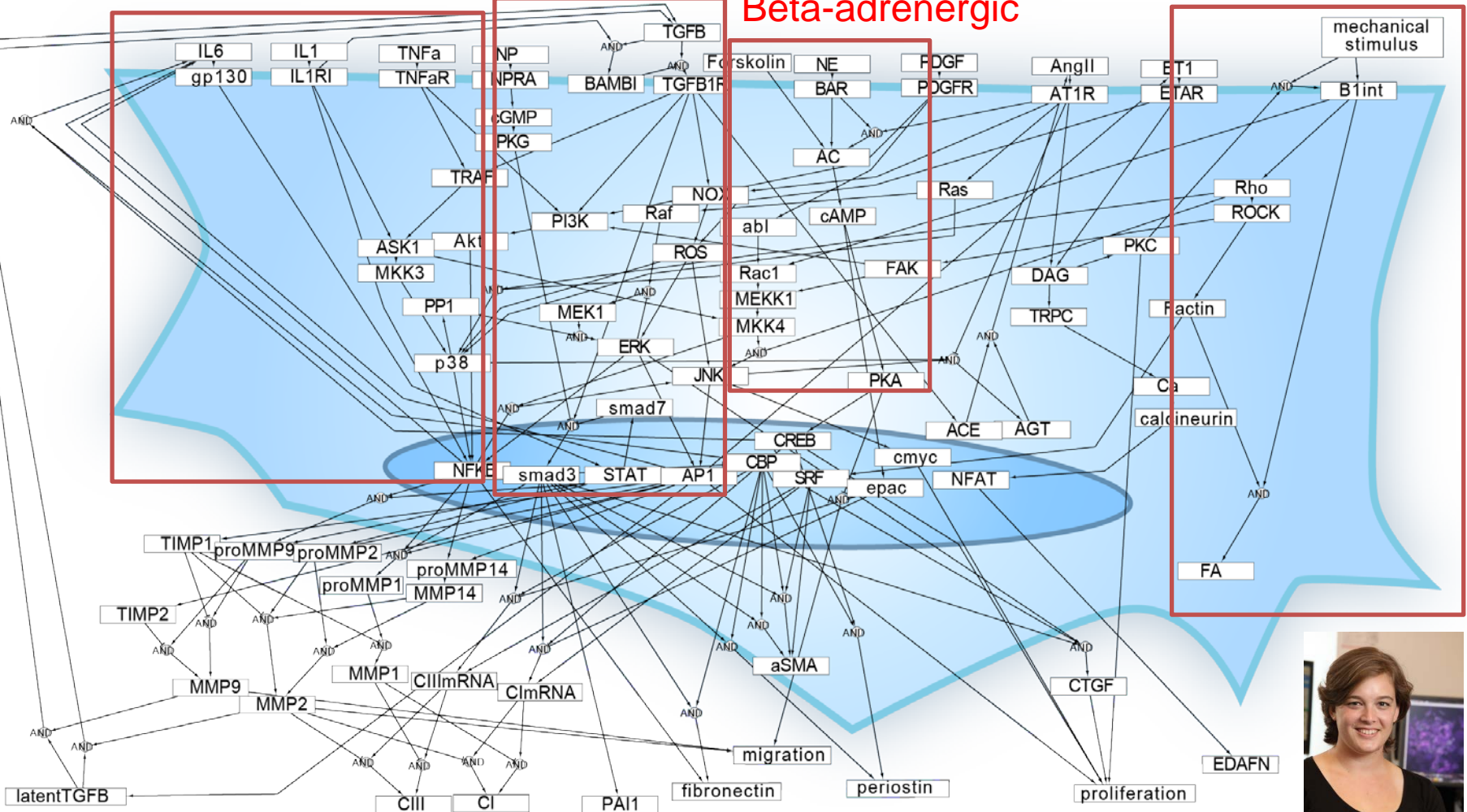
# Reconstruction of the fibroblast signaling network

Cytokines

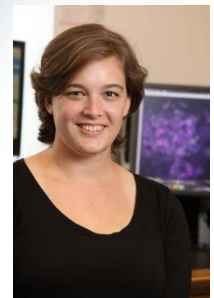
TGFβ

Beta-adrenergic

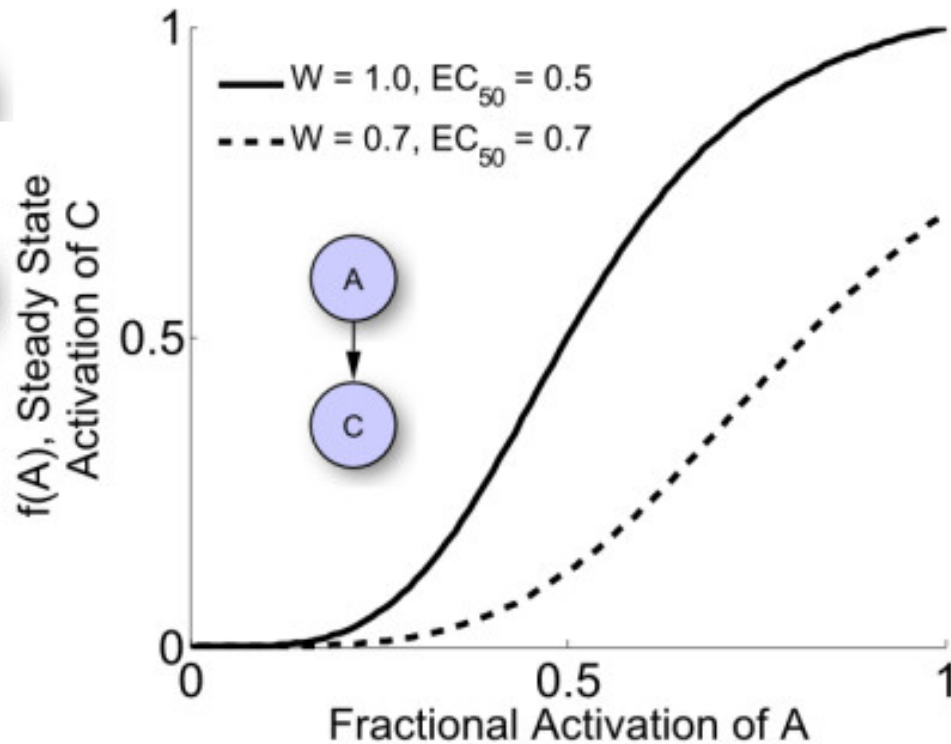
Integrin



89 nodes, 129 reactions reconstructed from 177 papers  
 2+ citations per reaction, emphasis on cardiac fibroblasts

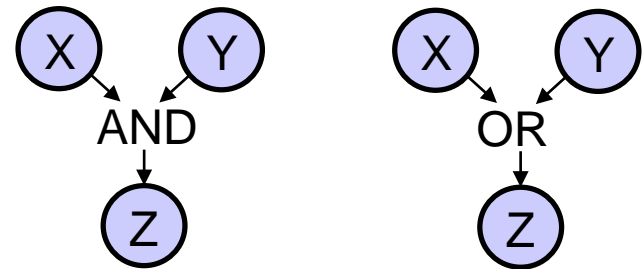


# From network structure to dynamics: logic-based differential equations



$$f_{act}(A) = \frac{A^n}{EC_{50}^n + A^n}$$

$$\frac{dC}{dt} = \frac{1}{\tau_C} (W_{AC} f_{act}(A) Y_{MAX,C} - C)$$

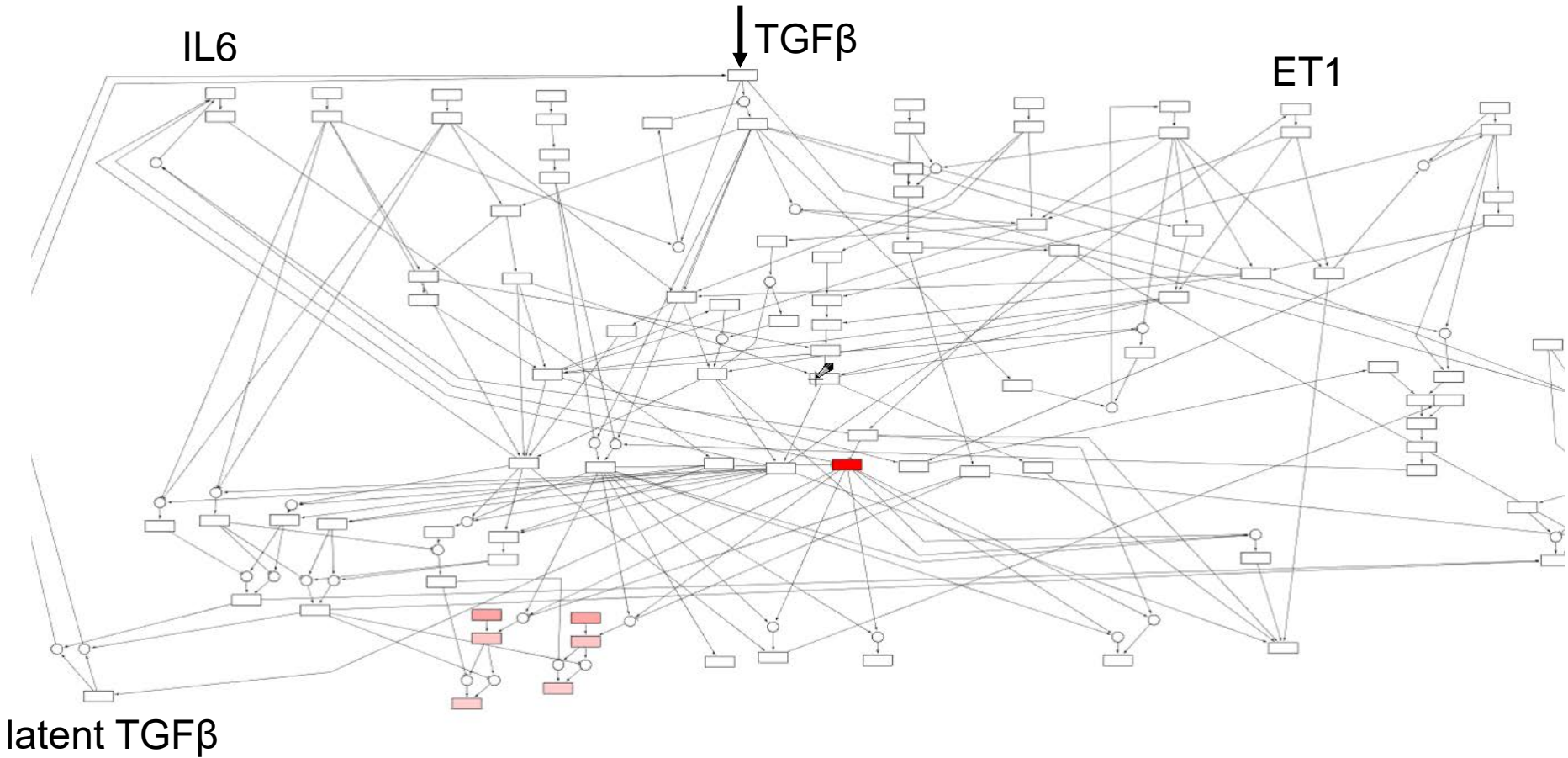


$$AND(X, Y) = f(X)f(Y)$$

$$OR(X, Y) = f(X) + f(Y) - f(X)f(Y)$$

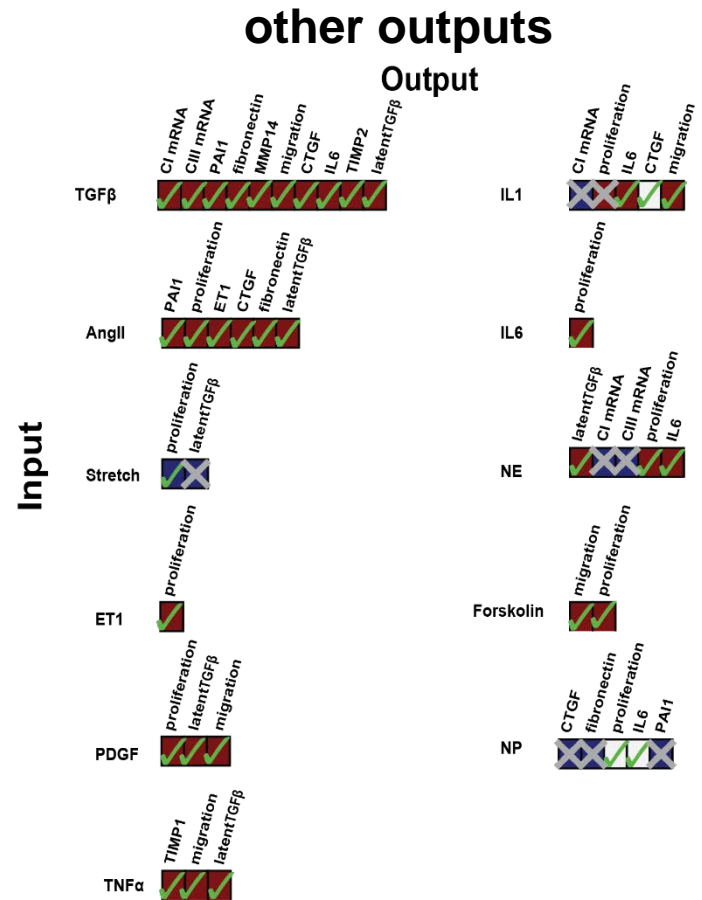
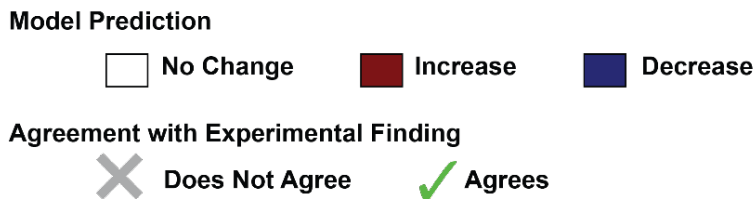
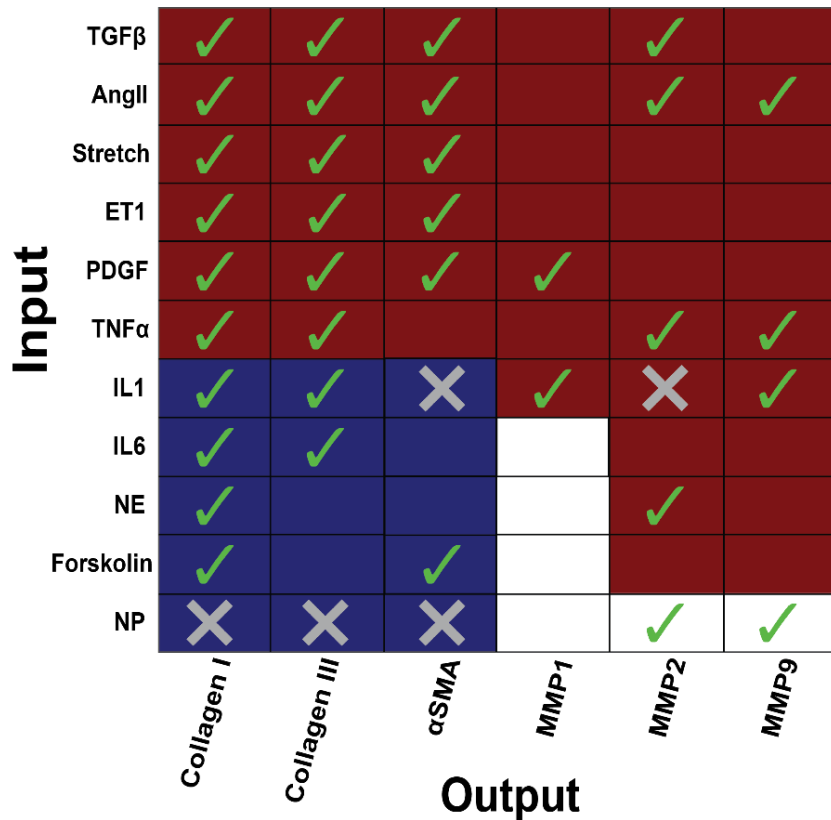
- Proteins/genes in units of normalized activity, not concentration
- Reactions use normalized-Hill functions and AND/OR logic gates.
- Default parameter values:  $EC_{50}, (0.5)$ , Hill coeff (1.4), rxn weight (1) time constant (signaling: 10 s, transcription: 1 h, translation: 10 h)

# Predicted network response to TGFβ



Logic-based differential equation model

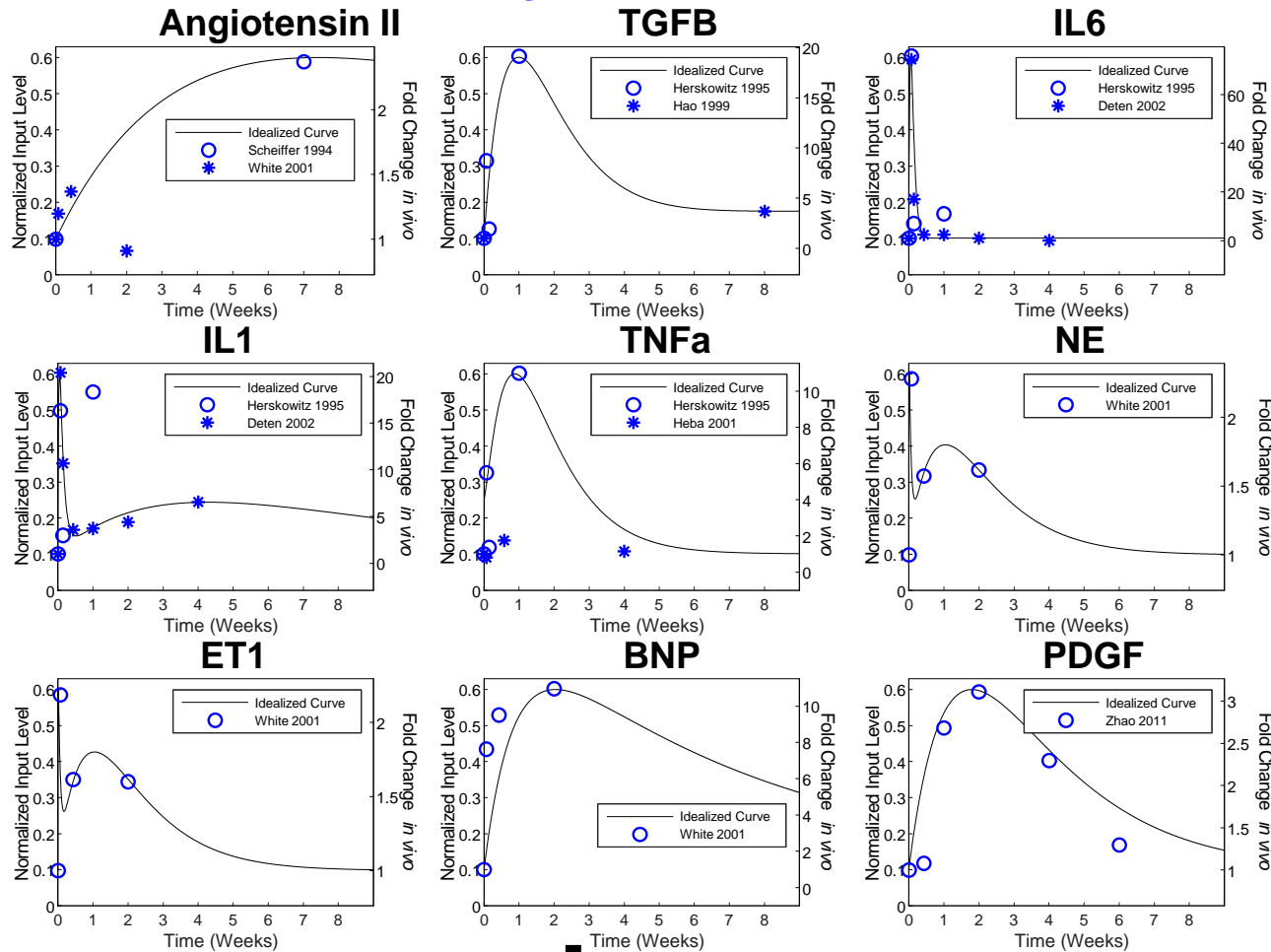
# Model accurately predicts 66 of 82 input-output relationships



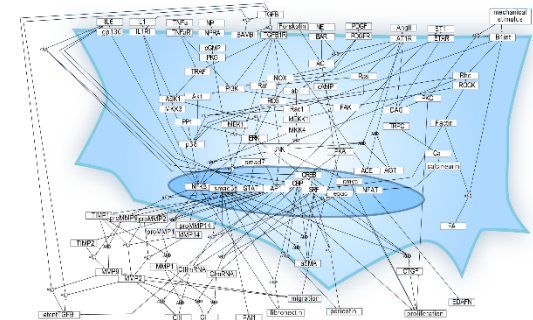
Cardiac fibroblast validation data from 34 papers not used for model building  
 Validation accuracy = 80%; **see poster**



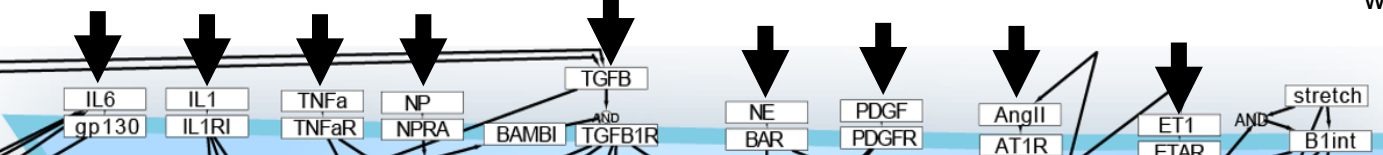
# Applying the network model to predict matrix remodeling dynamics after myocardial infarction



9 model inputs driven by experimentally measured cytokine/hormone dynamics after myocardial infarction

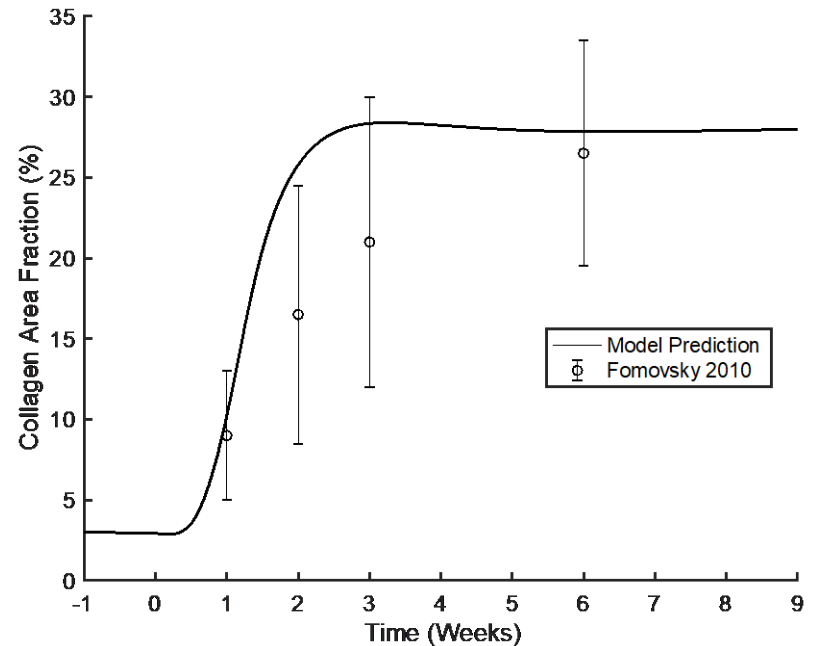
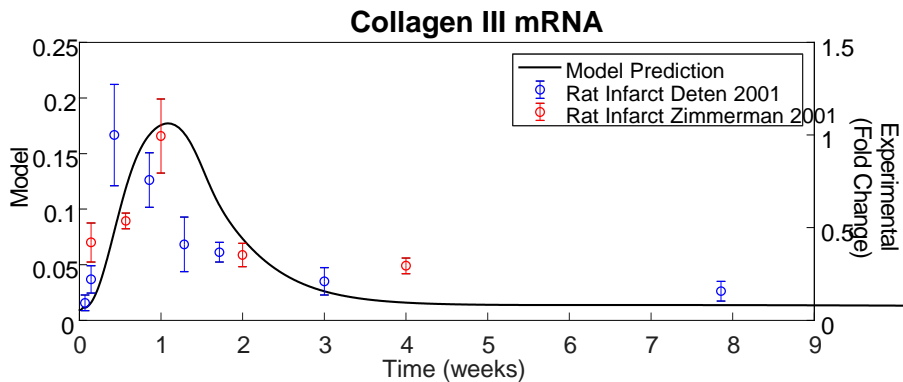
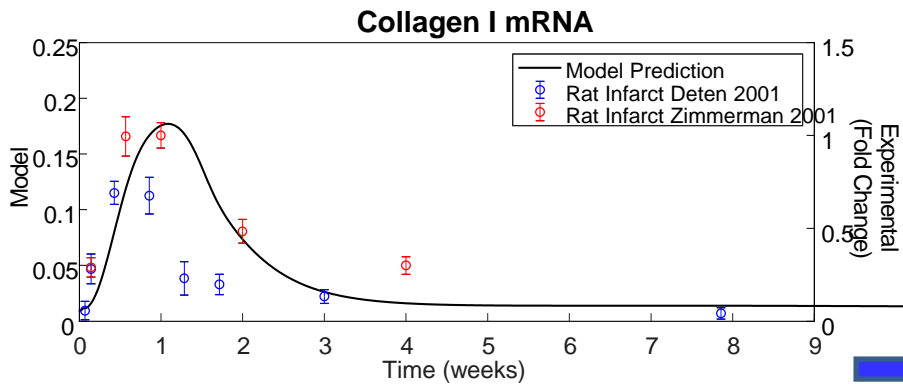


Post-MI experimental data from rat or human hearts, from infarct zone where available





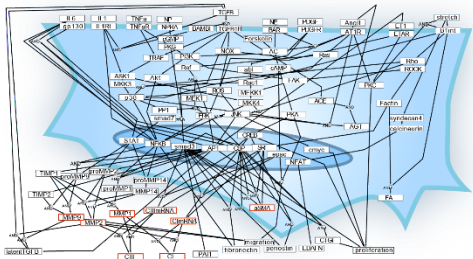
# Experimental validation of predicted collagen mRNA and protein outputs after myocardial infarction



Network model coupled to single ODE model with experimentally measured time-dependent MMP activity and fibroblast proliferation

Experimental data from rat infarcts:  
Deten 2001  
Zimmerman 2001  
Fomovsky 2010

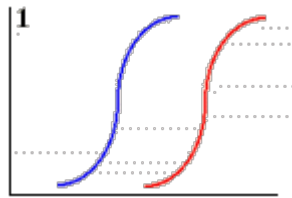
# Simulating FDA approved drugs targeting fibroblast signaling network



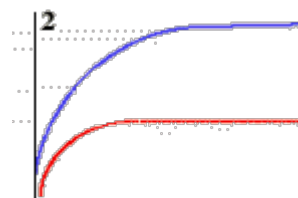
25 FDA approved drugs that uniquely target 24 network nodes

Competitive inhibitors/activators

Non-competitive inhibitors/activators



shift [X]

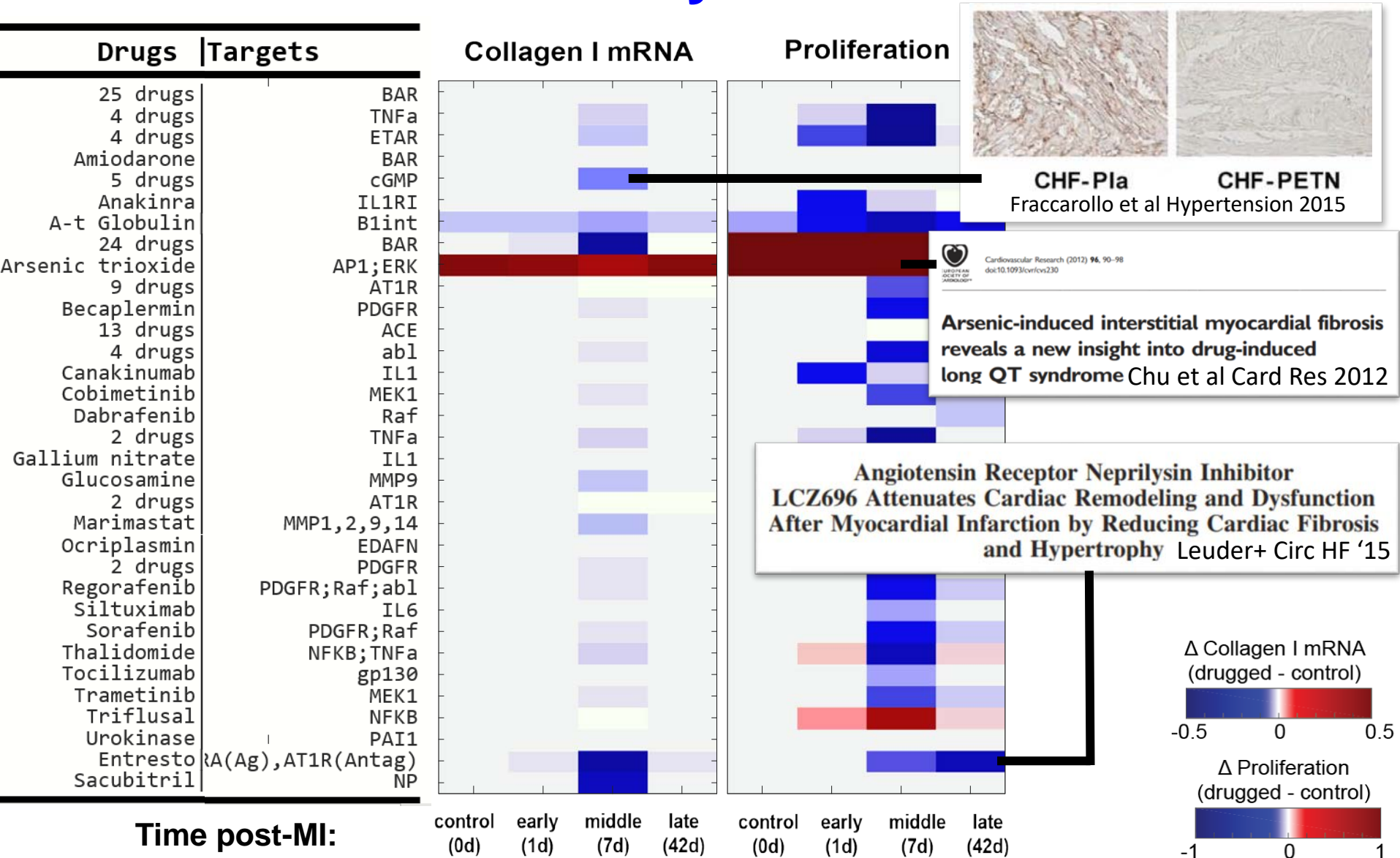


adjust reaction weights

Drugs	Binding	Agonism	Targets
25 drugs	Competitive	Antagonist	BAR
4 drugs	Non-Competitive	Antagonist	TNFa
4 drugs	Competitive	Antagonist	ETAR
Amiodarone	Non-Competitive	Antagonist	BAR
5 drugs	Non-Competitive	Agonist	cGMP
Anakinra	Competitive	Antagonist	IL1RI
A-t Globulin	Non-Competitive	Antagonist	B1nt
24 drugs	Competitive	Agonist	BAR
Arsenic trioxide	Competitive	Agonist	AP1;ERK
9 drugs	Competitive	Antagonist	AT1R
Becaplermin	Competitive	Antagonist	PDGFR
13 drugs	Competitive	Antagonist	ACE
4 drugs	Non-Competitive	Antagonist	abl
Canakinumab	Competitive	Antagonist	IL1
Cobimetinib	Competitive	Antagonist	MEK1
Dabrafenib	Non-Competitive	Antagonist	Raf
2 drugs	Competitive	Antagonist	TNFa
Gallium nitrate	Non-Competitive	Antagonist	IL1
Glucosamine	Non-Competitive	Antagonist	MMP9
2 drugs	Non-Competitive	Antagonist	AT1R
Marimastat	Competitive	Antagonist	MMP1,2,9,14
Ocriplasmin	Non-competitive	Antagonist	EDAFN
2 drugs	Non-Competitive	Antagonist	PDGFR
Regorafenib	Non-Competitive	Antagonist	PDGFR;Raf;abl
Siltuximab	Competitive	Antagonist	IL6
Sorafenib	Non-competitive	Antagonist	PDGFR;Raf
Thalidomide	Non-Competitive	Antagonist	NFKB;TNFa
Tocilizumab	Competitive	Antagonist	gp130
Trametinib	Non-Competitive	Antagonist	MEK1
Triflusal	Non-Competitive	Antagonist	NFKB
Urokinase	Non-Competitive	Antagonist	PAI1
Entresto	Competitive	Both	NPRA(Ag),AT1R(Antag)
Sacubitril	Non-Competitive	Agonist	NP

Dose: 80% of saturation

# Virtual screen for drugs that modulate fibroblasts after myocardial infarction

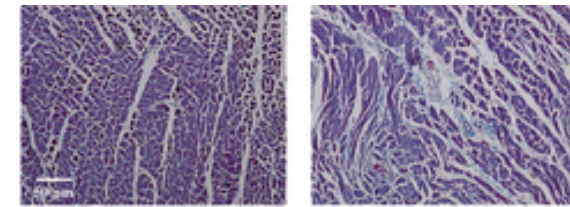


# Network mechanisms contributing to fibrosis induced by arsenic trioxide

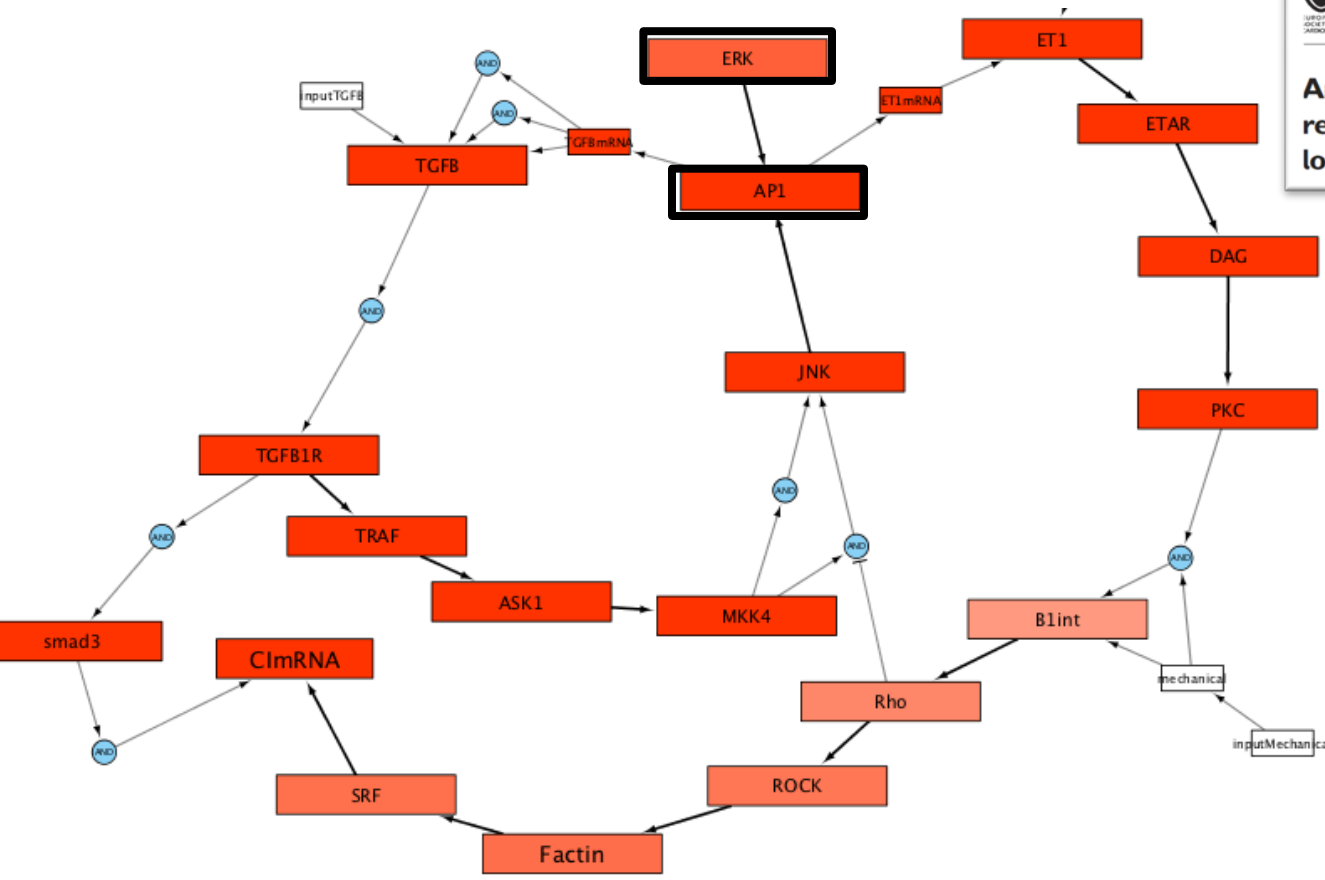
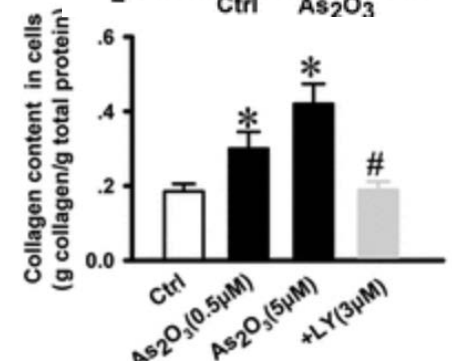
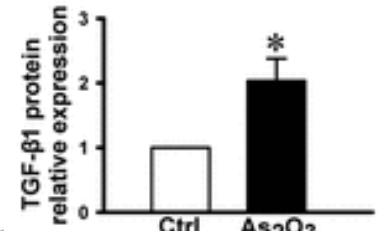
Cardiovascular Research (2012) 96, 90-98  
doi:10.1093/cvr/cvs230

**Arsenic-induced interstitial myocardial fibrosis reveals a new insight into drug-induced long QT syndrome**

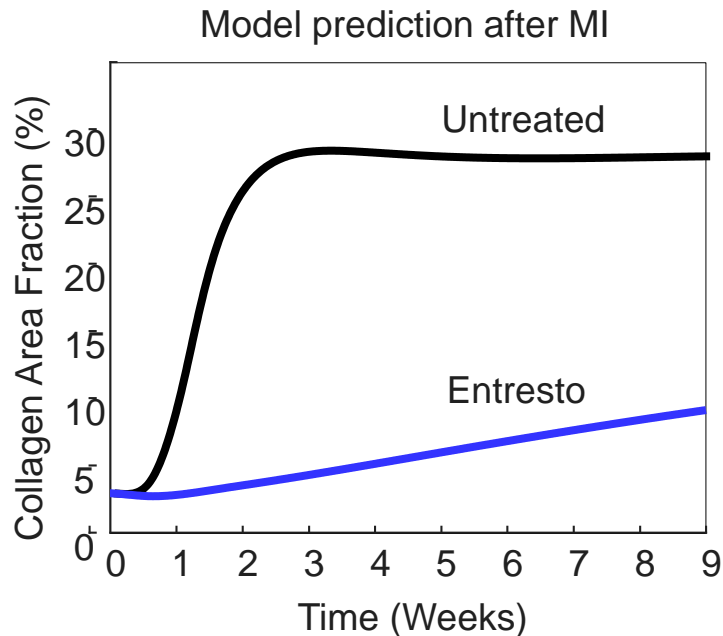
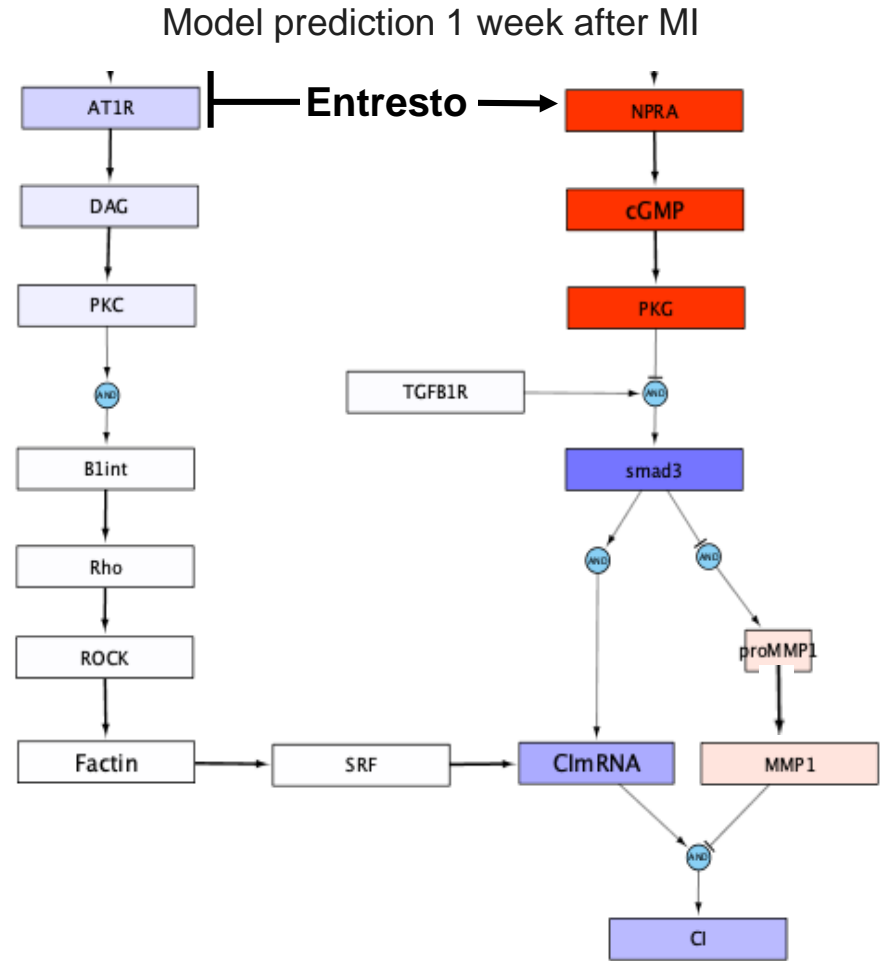
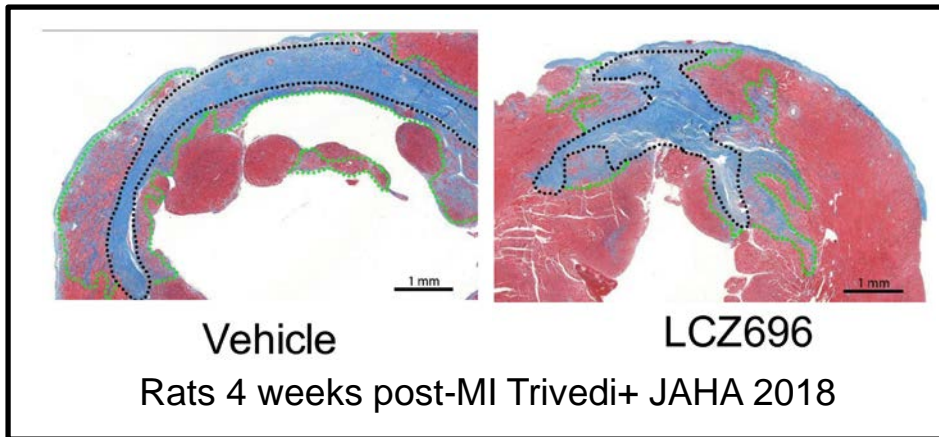
Chu et al Card Res 2012



Ctrl As<sub>2</sub>O<sub>3</sub>



# Network mechanisms contributing to fibrosis attenuated by Entresto



# Integrated agent-based and signaling network model of fibrosis

## Extracellular Space (Value layers)

Collagen, latent TGF $\beta$ , active TGF $\beta$ , IL-1 $\beta$ , IL-6, TNF $\alpha$

Parameters: Activation rate, Degradation rate



### Agent

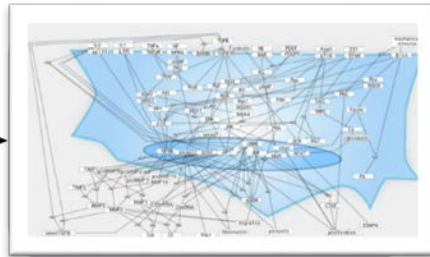
Fibroblast

### Attributes

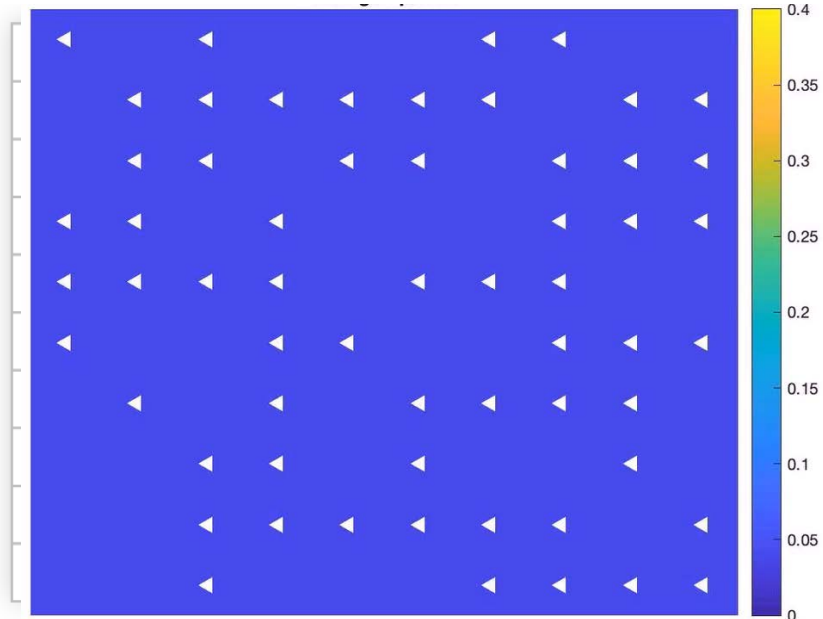
Location  
Network State

### Methods

Get input from extracellular space  
Update network state  
Secrete latent TGF $\beta$  and IL-6  
Deposit collagen  
Move



Fibrotic



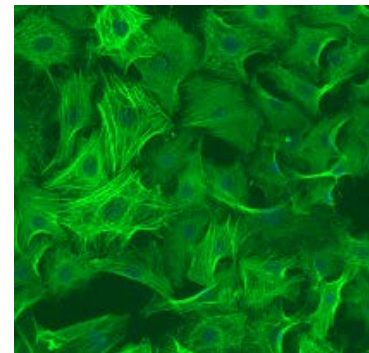
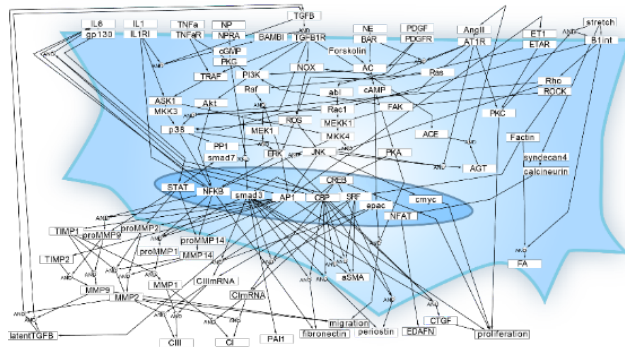
Inflammatory

Michaela Rikard  
w. Peirce-Cottler, Holmes



# Summary

- Developed and validated a large-scale model of cardiac fibroblast signaling
- Validated model prediction that stretch-mediated myofibroblast differentiation involves a TGF $\beta$  autocrine loop
- Framework for predicting in vivo signaling dynamics and effects of drugs after myocardial infarction
- Predicted pro- and anti-fibrotic FDA approved drugs (e.g. arsenic trioxide, nitrates, Entresto)



# Acknowledgements

 @sauce\_lab

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**Shayn Peirce-Cottler (UVA)**

**Michaela Rikard (UVA)**

**Will Richardson (Clemson)**

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Posters on automated validation, fibrosis gene therapies

Grad student and post-doc positions available  
<http://bme.virginia.edu/saucerman>



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