## Aaron S. Meyer Research and Teaching Plans

Aaron Meyer University of California, Los Angeles March 20, 2017

> Research Focus 1 Research Focus 2 Timeline Teaching





# Cell signaling is complex, and challenging to apply toward a desired goal



# Cell signaling is complex, and challenging to apply toward a desired goal







Drive: Metastasis, resistance (RF2), immunosuppression



Drive: Metastasis, resistance (RF2), immunosuppression

- Molecular model
  - Identify what matters in vivo
- Tool compounds



Drive: Metastasis, resistance (RF2), immunosuppression

- Molecular model
- Identify what matters in vivo
- Tool compounds





Drive: Metastasis, resistance (RF2), immunosuppression

Outcomes:

- Molecular model
- Identify what matters in vivo
- Tool compounds



Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS



Drive: Metastasis, resistance (RF2), immunosuppression

- Molecular model
- Identify what matters in vivo
- Tool compounds







Drive: Metastasis, resistance (RF2), immunosuppression

Outcomes:

- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based)





Drive: Metastasis, resistance (RF2), immunosuppression

- Outcomes:
- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)





Drive: Metastasis, resistance (RF2), immunosuppression

Outcomes:

- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)

Aim 2: Utilize mechanistic kinetic modeling to identify the effects of differing TAMR targeting strategies





Drive: Metastasis, resistance (RF2), immunosuppression

Outcomes:

- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)

Aim 2: Utilize mechanistic kinetic modeling to identify the effects of differing TAMR targeting strategies Assemble full model





Drive: Metastasis, resistance (RF2), immunosuppression

Outcomes:

- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)

Aim 2: Utilize mechanistic kinetic modeling to identify the effects of differing TAMR targeting strategies Assemble full model Predict inhibition effects





Drive: Metastasis, resistance (RF2), immunosuppression

- Outcomes:
- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)

Aim 2: Utilize mechanistic kinetic modeling to identify the effects of differing TAMR targeting strategies Assemble full model Predict inhibition effects Validate inhibition *in vitro* 





Drive: Metastasis, resistance (RF2), immunosuppression

- Outcomes:
- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)

Aim 2: Utilize mechanistic kinetic modeling to identify the effects of differing TAMR targeting strategies Assemble full model Predict inhibition effects Validate inhibition *in vitro* 

Aim 3: Validate model-predicted targeting *in vivo* by comparing the effects of fragment inhibitors to existing agents





Drive: Metastasis, resistance (RF2), immunosuppression

- Outcomes:
- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)

Aim 2: Utilize mechanistic kinetic modeling to identify the effects of differing TAMR targeting strategies Assemble full model Predict inhibition effects Validate inhibition *in vitro* 

Aim 3: Validate model-predicted targeting *in vivo* by comparing the effects of fragment inhibitors to existing agents Treat 4T1 tumors





Drive: Metastasis, resistance (RF2), immunosuppression

- Outcomes:
- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)

Aim 2: Utilize mechanistic kinetic modeling to identify the effects of differing TAMR targeting strategies Assemble full model Predict inhibition effects Validate inhibition *in vitro* 

Aim 3: Validate model-predicted targeting *in vivo* by comparing the effects of fragment inhibitors to existing agents Treat 4T1 tumors Measure tumor environment effects





Drive: Metastasis, resistance (RF2), immunosuppression

- Outcomes:
- Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)

Aim 2: Utilize mechanistic kinetic modeling to identify the effects of differing TAMR targeting strategies Assemble full model Predict inhibition effects Validate inhibition *in vitro* 

Aim 3: Validate model-predicted targeting *in vivo* by comparing the effects of fragment inhibitors to existing agents Treat 4T1 tumors Measure tumor environment effects Regress against metastasis





Drive: Metastasis, resistance (RF2), immunosuppression

- Outcomes:
  - Molecular model
- Identify what matters in vivo
- Tool compounds

Aim 1: Express TAMR receptor fragments and quantitatively characterize the binding to Gas6/ProS Measure Ig affinities: (plate-based, SPR) Competition experiments (plate-based) Compare to full-length receptor (SPR)

Aim 2: Utilize mechanistic kinetic modeling to identify the effects of differing TAMR targeting strategies Assemble full model Predict inhibition effects Validate inhibition *in vitro* 

Aim 3: Validate model-predicted targeting *in vivo* by comparing the effects of fragment inhibitors to existing agents Treat 4T1 tumors Measure tumor environment effects Regress against metastasis

Other areas of application: FcγRs, FGFRs, pattern receptors (e.g. TLRs), RET, type I interferons, etc.











- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification



Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification



Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance Evaluate resistance from AXL mutants/RTK panel

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification



Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance

Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification



Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance

Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement Model signaling to resistance relationship

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification



Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance

Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement Model signaling to resistance relationship Validate signaling to resistance predictions

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification



Outcomes:

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification

Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance

Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement Model signaling to resistance relationship Validate signaling to resistance predictions

Aim 2: Quantify the corresponding RTK interaction profiles to identify the requisite receptor-level interactions promoting resistance



Outcomes:

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification

Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement

Model signaling to resistance relationship Validate signaling to resistance predictions

Aim 2: Quantify the corresponding RTK interaction profiles to identify the requisite receptor-level interactions promoting resistance Quantify receptor-interacting proteins



Outcomes:

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification

Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement

Model signaling to resistance relationship Validate signaling to resistance predictions

Aim 2: Quantify the corresponding RTK interaction profiles to identify the requisite receptor-level interactions promoting resistance

Quantify receptor-interacting proteins Model adapter to signaling relationship



Outcomes:

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification

Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement Model signaling to resistance relationship

Validate signaling to resistance predictions

Aim 2: Quantify the corresponding RTK interaction profiles to identify the requisite receptor-level interactions promoting resistance

Quantify receptor-interacting proteins Model adapter to signaling relationship Validate adapters implicated in resistance



Outcomes:

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification

Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement

Model signaling to resistance relationship Validate signaling to resistance predictions

Aim 2: Quantify the corresponding RTK interaction profiles to identify the requisite receptor-level interactions promoting resistance

Quantify receptor-interacting proteins Model adapter to signaling relationship Validate adapters implicated in resistance

Aim 3: Evaluate multiplexed protein interaction measurement as an effective method to predict resistance mechanism



Outcomes:

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification

Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement

Model signaling to resistance relationship Validate signaling to resistance predictions

Aim 2: Quantify the corresponding RTK interaction profiles to identify the requisite receptor-level interactions promoting resistance

Quantify receptor-interacting proteins Model adapter to signaling relationship Validate adapters implicated in resistance

Aim 3: Evaluate multiplexed protein interaction measurement as an effective method to predict resistance mechanism Validate PLA assay



Outcomes:

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification

Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement

Model signaling to resistance relationship Validate signaling to resistance predictions

Aim 2: Quantify the corresponding RTK interaction profiles to identify the requisite receptor-level interactions promoting resistance

Quantify receptor-interacting proteins Model adapter to signaling relationship Validate adapters implicated in resistance

Aim 3: Evaluate multiplexed protein interaction measurement as an effective method to predict resistance mechanism Validate PLA assay

Identify drug combinations (xenograft samples)



#### Outcomes:

- Map resistance signaling
- Detailed AXL signaling
- Precise combination therapy identification

Aim 1: Map the global signaling state changes during switched RTK activation to identify the essential features of bypass resistance Evaluate resistance from AXL mutants/RTK panel Phosphoproteomic measurement Model signaling to resistance relationship

Validate signaling to resistance predictions

Aim 2: Quantify the corresponding RTK interaction profiles to identify the requisite receptor-level interactions promoting resistance

Quantify receptor-interacting proteins Model adapter to signaling relationship Validate adapters implicated in resistance

Aim 3: Evaluate multiplexed protein interaction measurement as an effective method to predict resistance mechanism

- Validate PLA assay
- Identify drug combinations (xenograft samples) Test combination predictions

Timeline   2017/2018 2018/2019 2019/2020 2020/2021				
2017/2010	2010/2013	2013/2020		
Existing Funding: \$320,000/y	r (DP5, Brodeur, AMIGOS)	P	ostdoc Graduate Student Undergraduate	
Research Focus 1 Submitted Funding Applications: Bu	rroughs Wellcome CASI (current finalis	st)		
Aim 1: Measure Binding				
Aim 2:	: Model Assembly/Validat	ion		
Existing postdoc		Aim 3: In vivo Applicatior	ו	
FcγR models				
<b>Research Focus 2</b> Submitted Funding Application: NC	I Cancer Systems Biology Consortium	U01		
Aim 1: Identify essenti	al bypass signaling			
Aim 2: Identify driving RTK-adapter interactions				
		Aim 3: Apply PLA	to predict drug combinations	
Existing postdoc				
Growth models with apoptosis/n	necroptosis			

#### **Teaching Plans**

#### Existing courses to which I could immediately contribute:

Undergraduate	Graduate
BE 100: Bioengineering Fundamentals	BE 295E - Seminar: Research Topics in BE –
BE 110: Biotransport and Bioreaction Processes	Molecular Cell BE Research
BE 167L: Bioengineering Laboratory	BE C201: Engineering Principles for Drug Delivery
BE 188 - Special Courses in BE: Cell Engineering	

#### Suggested course development:

#### Applying data-driven modeling in bioengineering

- Each week:
  - Lecture on a method
  - Discussion of paper using the method paired with experiments
  - Implementation
- Reproducible methods and tooling emphasized throughout
- Final project re-implementing a study from literature with documentation, data, testing & code
- Appropriate as upper-level undergraduate or graduate course