Modern Medicine is Built on Antibiotics

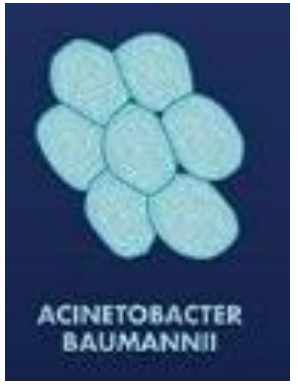
Mark Plummer, PhD

Yale Center for Molecular Discovery

Former project leader Pfizer Antibacterials

Robert Bonomo, M.D., Case Western is a widely recognized authority on testing antibacterial agents and beta lactamases.

Brad Spellberg, M.D. USC is a leading world authority on bacterial resistance and excellent *in vivo* model expertise.



BLAVATNIK Fund for Innovation at Yale

Keep the Antibiotic Miracle Alive

BLAVATNIK Fund for Innovation at Yale

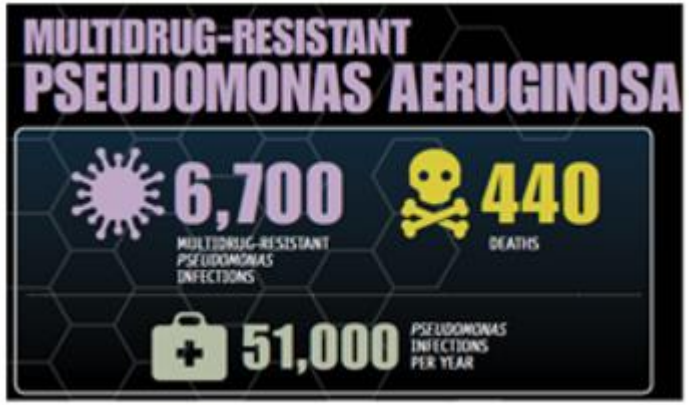
The Problem---Resistant Gram negative infections

The Market: Substantial, Continuously growing

Elderly, immune modulator treated, transplant or oncology patients, CF patients ---all highly susceptible to infection

The Competition: Low

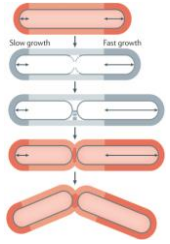
The Need: Evergreen



Two Remarkable Assets

BLAVATNIK Fund for Innovation at Yale

- **Two series of novel non beta lactam PBP inhibitors that show remarkable activity against resistant current Gr- clinical isolates**
- **The YU434 series is a broad agent against many Gr- pathogens while YU911 is a narrow agent with best activity against Acenitobacter baumannii**
- **Low susceptibility to Class A, B, C, D beta-lactamase hydrolysis –circumventing a major cause of resistance**
- **Both series have drug like attributes similar to current hospital use IV antibiotics**
- **YU434 has attributes suitable for treating Pa in CF patients**
- **Patents have been filed securing IP**



Bacterial cell division

- PBPs are enzymes essential for bacterial cell wall homeostasis, synthesis and division.

MIC Values Against Difficult to Treat Isolates

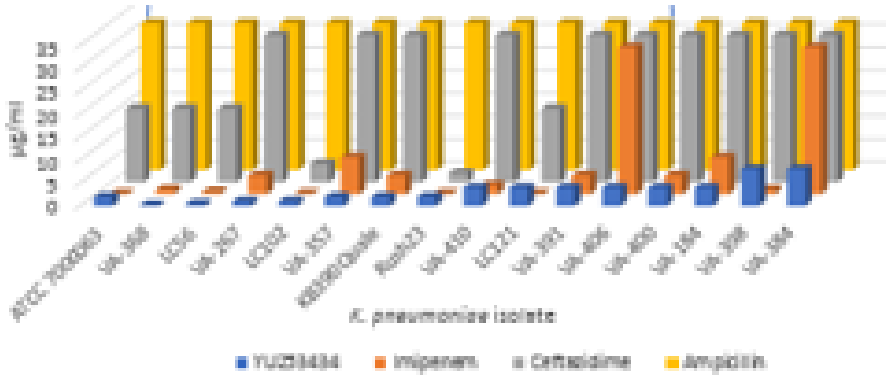
BLAVATNIK Fund for Innovation at Yale

YU434 MIC_{50} and MIC_{90} versus comparator antibiotics for 200 *P. aeruginosa* isolates.

Compound	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
YU253434	1	8
Ceftazidime	4	>16
Ceftaz/Avi	4	>32
Aztreonam	8	>16
Meropenem	2	>8

YU434 MIC_{50} and MIC_{90} versus comparator antibiotics for 100 *K. pneumoniae* isolates.

Compound	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
YU253434	1	4
Aztreonam	>32	>32
Ceftazidime	16	>64
Meropenem	16	>64



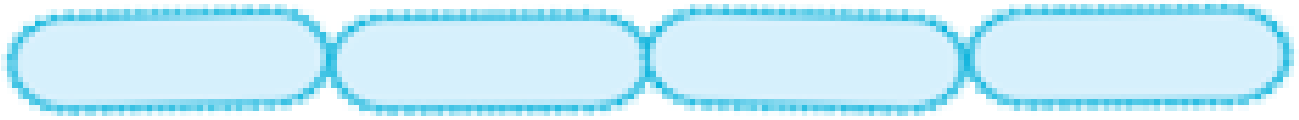
MIC_{50} and MIC_{90} for YU911 comparator antibiotics for 200 *Acinetobacter spp.*

Compound	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
YU253911	0.5	>16
Imipenem*	2	>8
Meropenem*	4	>8
Doripenem*	>2	>2
Ceftazidime*	16	>16
Cefepime*	16	>16
Aztreonam*	>16	>16
Amp/Sul*	<=8/4	>=16/8
Tigecycline*	1	1
Colistin*	0.5	2

Drug-like Properties for Treating CF or Hospital Infections

BLAVATNIK Fund for Innovation at Yale

- Solubility > 100 uM at pH7.4 in PBS
- Human and mouse microsome stability ‘434 >60 min, ‘911 >60 min
- P450 inhibition YU434 (8 CYPs) No inhibition; YU911 CYP2B6 IC50 = 110uM, (7 CYPS) No inhibition
- No Toxicity in human hepatocytes at 100uM (+4 others cell lines –YCMD)
- Off target screening against 43 enzymes and receptors--- Clean
- hERG no inhibition for YU434 nor YU911 at 30uM
- Testing against 10 other ion channels showed no activity at 30uM



IV Dosing in Mice Gives PK Similar to Other Hospital Use Agents

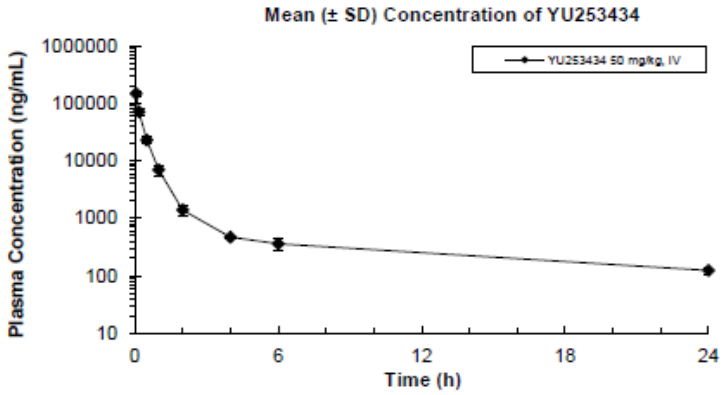
BLAVATNIK Fund for Innovation at Yale

YU434 blood levels remain >1ug/mL, above MIC50 at 2 hours similar to clinical agents

Table 1b. The plasma PK parameters after IV administration in mice:

Animal	$t_{1/2}$ (h)	C_0 (ng/mL)	AUClast (h*ng/mL)	AUCInf (h*ng/mL)	AUC Extr (%)	MRT (h)	Vss (L/kg)	CL (mL/min/kg)
IV-Mouse	11	200844	55866	57791	3	3	2	14

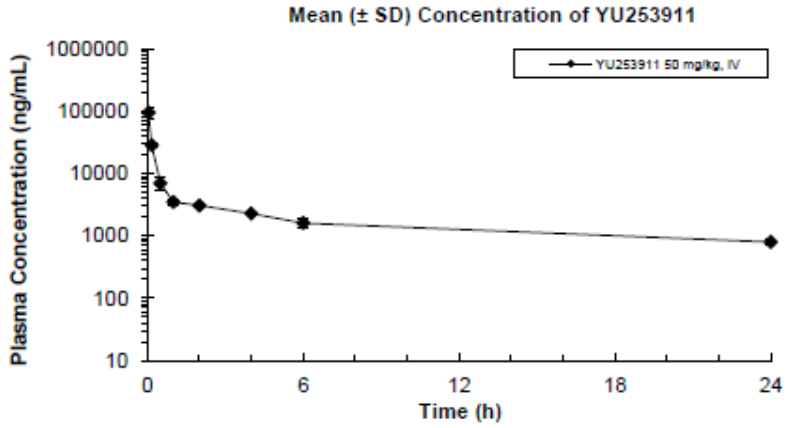
Figure 1. The mean plasma concentration-time profile of YU253434 after IV (50 mg/kg) administration in mice:



YU911 blood levels remain >1ug/mL, above MIC50 at 6 hours better than many clinical agents

Animal	$t_{1/2}$ (h)	C_0 (ng/mL)	AUClast (h*ng/mL)	AUCInf (h*ng/mL)	AUC Extr (%)	MRT (h)	Vss (L/kg)	CL (mL/min/kg)
IV-Mouse	15	159069	55972	72839	23	15	10	11

Figure 3. The mean plasma concentration-time profile of YU253911after IV (50 mg/kg) administration in mice:



Additional Investment Priorities to Enable Clinical Candidacy as Recommended by Potential Pharma Partners

BLAVATNIK Fund for Innovation at Yale

- **Utilize YU434 and YU911 in suitable in vivo efficacy studies such as thigh and lung infection models against multiple Gr- strains**

---Cost: 1 Compound X 1 mouse model = $40K, 1 compound X 2 models or 2 compounds X 1 model = $80K etc.

- **Find in vivo acute dose limits for toxicity**

---Cost: 1 Compound escalating dose IV = $5K

- **Understand resistance profile and causes**

--- Cost: 1 Compound $40K

Modern Medicine is Built on Antibiotics

---Keep the Antibiotic Miracle Alive