MEDI-573

MedImmune, LLC

Agenda

Background & MEDI-573 Preclinical Data	**Robert Sikorski, MD, PhD** Senior Director, Clinical Development MedImmune, LLC
MEDI-573 Clinical Data	**Jaye Viner, MD, MPH** Associate Director, Clinical Development MedImmune, LLC
MEDI-573 in Pediatric Settings & Conclusion	**Robert Sikorski, MD, PhD**

External Advisor

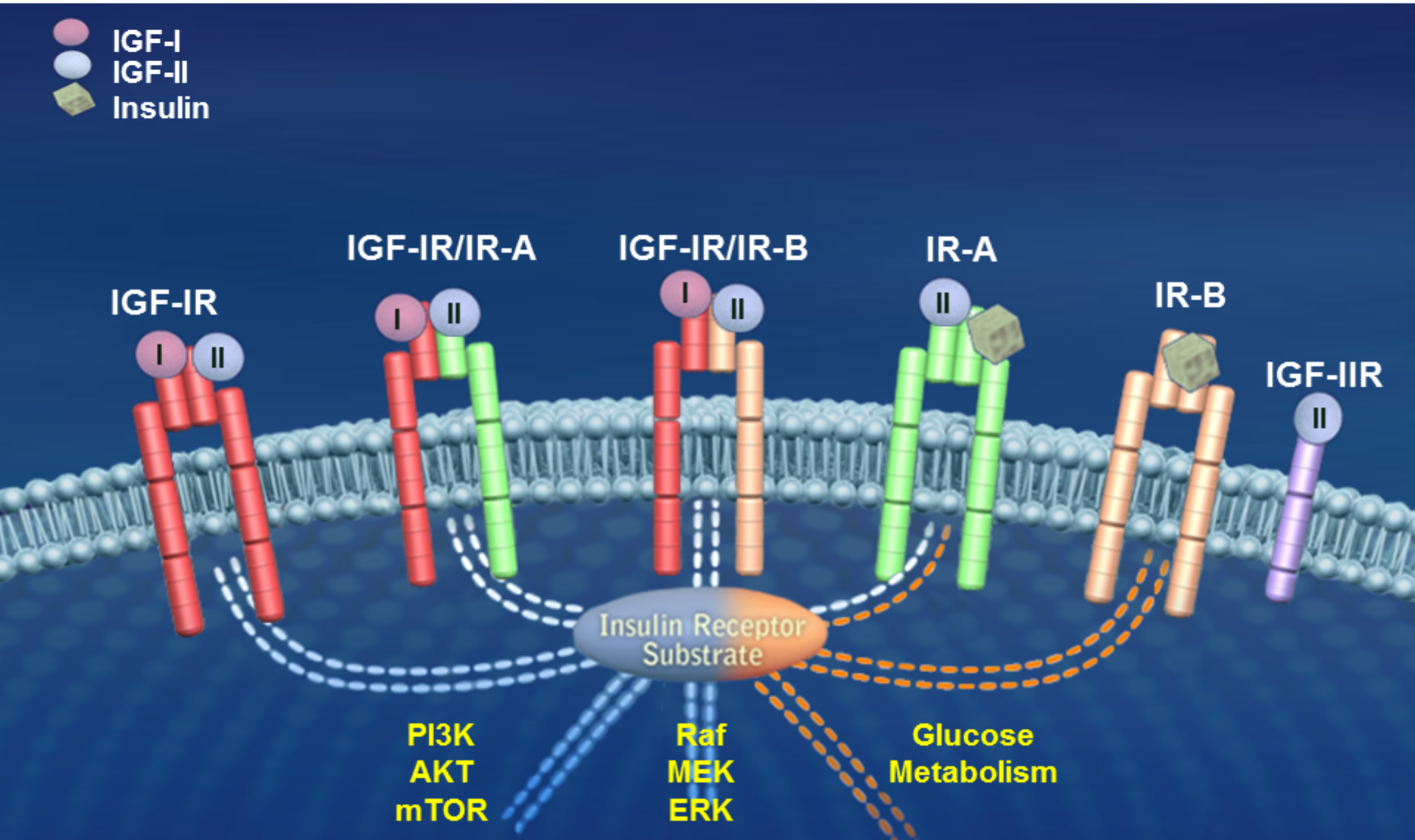
Katherine A. Janeway, MD
Dana Farber Cancer Institute-Children's Hospital, Boston

St. Baldrick's Foundation Scholar, Attending Physician, Pediatric Oncology

Background & MEDI-573 Preclinical Data

Robert Sikorski, MD, PhD

The Insulin-like Growth Factor (IGF) Pathway



IGF Pathway Inhibitors Tested in Clinical Trials

Antibodies	Small Molecules
Active Development	
Ganitumab	Linsitinib
Dalotuzumab	AXL-1717
Cixutumumab	INSM-18/NDGA
Robatumumab	BMS-754807
BIIB022	
BI-836845	
MEDI-573	
Inactive Development	
Figitumumab	XL-228
rhuMab IGFR	
R1507	
AVE-1642	

Single Agent Objective Responses Achieved with IGF Targeting Agents

Objective Responses	IGF Targeting Agent
Non-Small Cell Lung Cancer	XL228*
Neuroendocrine Tumor	Ganitumab
Rhabdomyosarcoma	R1507*
Adipocytic Sarcoma	Cixutumumab
Desmoplastic Small Round Cell Tumor	Ganitumab
Ewing's Sarcoma	R1507*
	Figitumumab*
	Ganitumab
	Cixutumumab
	Robatumumab

* No longer in active development

Objective Responses in Ewing's Sarcoma with IGF Targeting Agents as Monotherapy

	Size	CR	PR	ORR
	N	N	N	%
R1507				
NCT00642941	115	1	10*	10.0
Ganitumab				
NCT00562380	12	1	1	16.7
NCT00563680	19	-	1	5.3
Figitumumab				
NCT00474760	16	1	1	12.5
NCT00560235	106	-	15	14.1
Cixutumumab				
NCT00609141	10	-	1	10.0
NCT00668148	17	-	2**	11.8
Robatumumab				
NCT00617890	25-50***	-	3	n/a

* In addition, 8 uPRs
**Progression-free rate (PFR) at 12 wks
***Connective Tissue Oncology Society 2008

Response Durations in Ewing's Sarcoma with IGF Targeting Agents as Monotherapy

Objective Responses

R1507:	Median 29 w (range 12-94 w)
Ganitumab:	1 CR > 30 m
Figitumumab:	1 CR 21.5 m
	1 PR 11.4 m
	Median 4.7 m (range 3.7-6.1 m)

Stable Disease*

R1507:	18 SD, median 11.4 w (range 5.6-30.1 w)
Ganitumab:	7 SD, 1 SD > 6 m
Figitumumab:	3 SD ≥ 9 m (up to 16+ m)
	1 SD ≥ 6 m
	2 SD ≥ 3 m
Cixutumumab:	4 SD ≥ 3 cycles** (median 7, range 3-11)

*SD was 15-40% across monotherapy trials
**Cycle length Q28D

Dose Limiting Toxicities (DLTs) Reported in Phase 1 Trials of IGF Targeting Agents

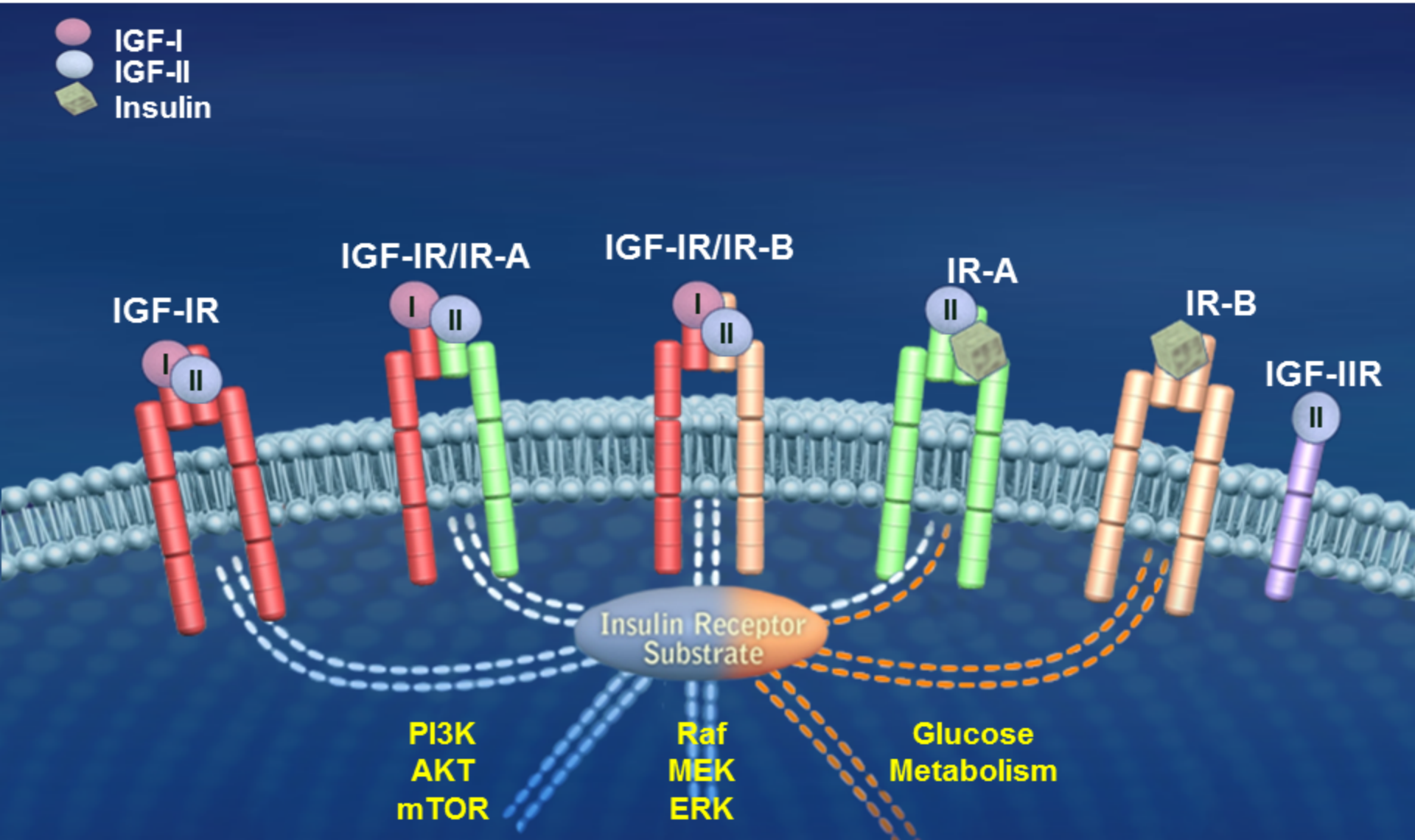
Agent	Accrual	DLTs	
Ganitumab	53	**Thrombocytopenia** (1, G3)	
Dalotuzumab	29	**Thrombocytopenia** (1, G4)	
Cixutumumab	15	-	
Figitumumab	24	-	
BIIB022	24	**QTc** (1, G3)	
Robatumumab	30	-	
R1507	36	-	
AVE-1642	14	-	
BMS-754807	19	-	
INSM-18	15	-	
AXL-1717	35	-	
XL-228	41	**Neutropenia** (3, G3/4)	
Linsitinib	118	Daily Dose (57): **Hyperglycemia** (2, G3) **Transaminasemia** (2, G3) **QTc prolongation** (1, G3) **Drug Delay** (1, G2)	Intermittent Dose (61): **Fatigue** (1, G4) **Hyperglycemia** (4, G3) **QTc prolongation** (1, G3) **Vomiting** (1, G3)

Figitumumab Phase 2 Trial in Colorectal Cancer: Safety Findings

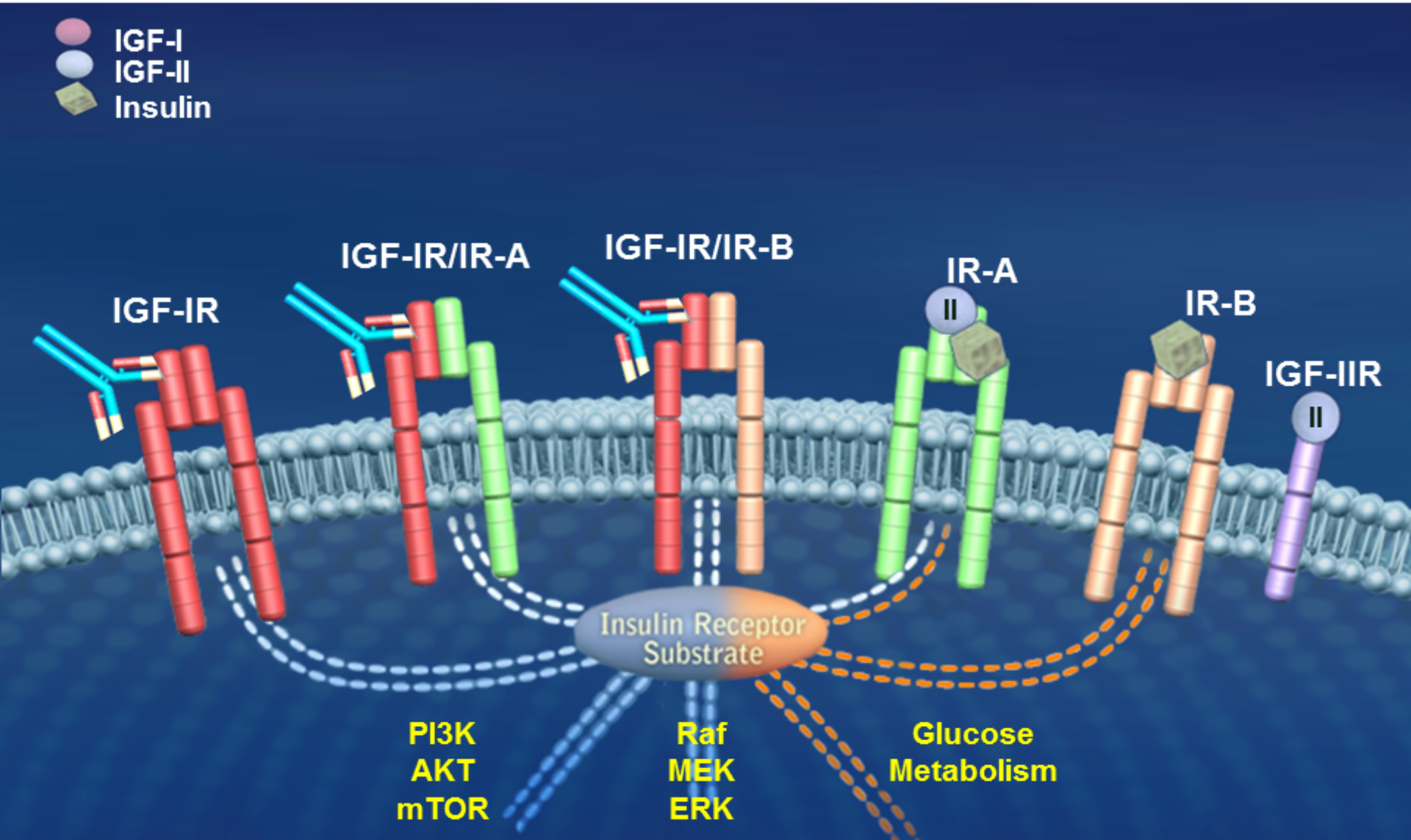
	20 mg/kg (N=79)		30 mg/kg (N=76)	
AE (%)*	Grade 3/4	Total	Grade 3/4	Total
Hyperglycemia	16	26	22	33
Asthenia	13	32	13	28
GGT increased	8	11	8	13
Fatigue	6	27	6	35
Lymphopenia	6	37	4	37
Anemia	5	68	3	58
Diarrhea	5	18	1	30
Abdominal pain	5	16	6	13
Lethargy	5	14	0	7
Vomiting	4	25	6	19
Back pain	1	19	6	15
Dehydration	1	5	6	11
Nausea	0	27	5	33

*Cut off at 5%; Becerra C et al. 2011 ASCO Annual Meeting (abst 3525)

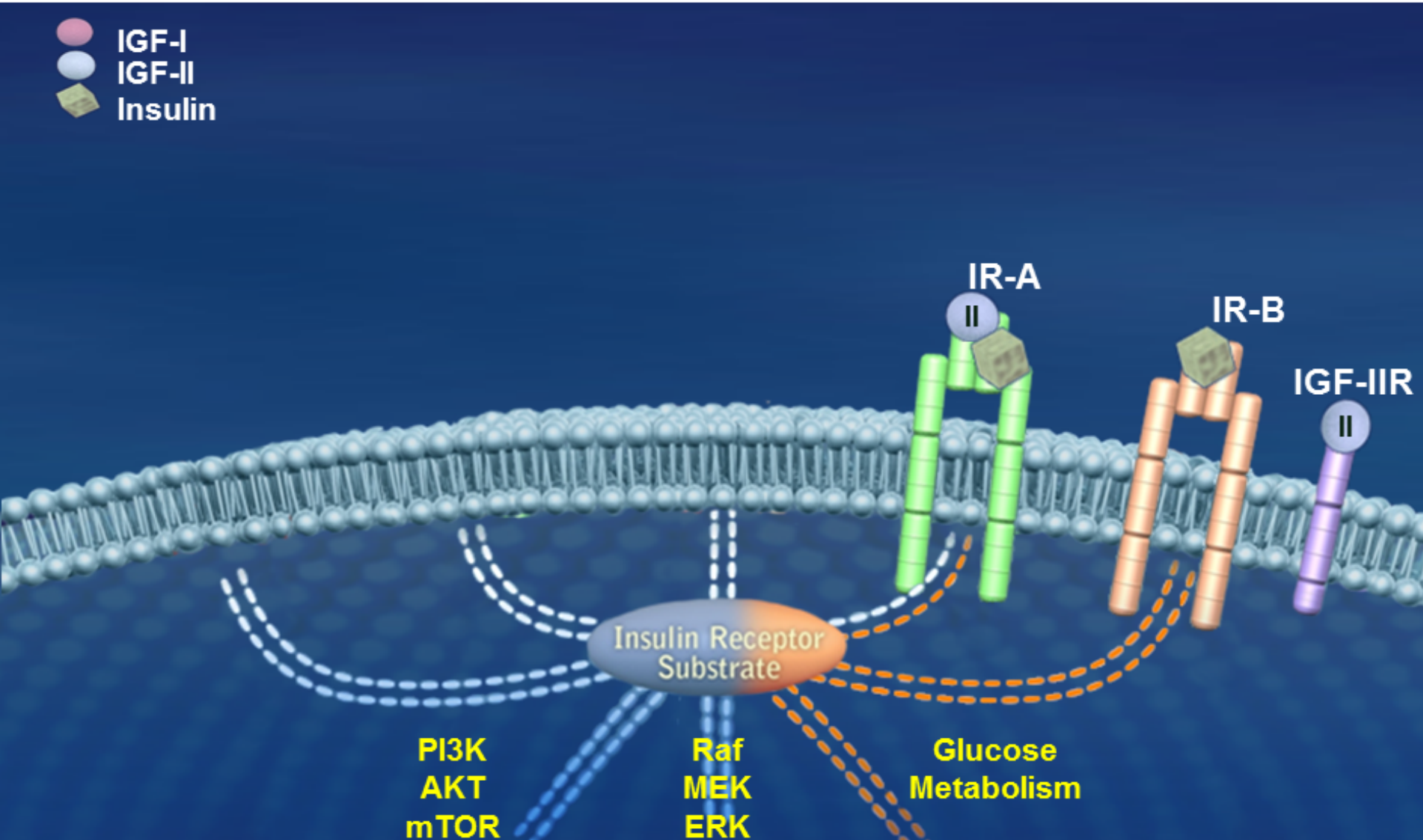
Challenges with Targeting the IGF Pathway



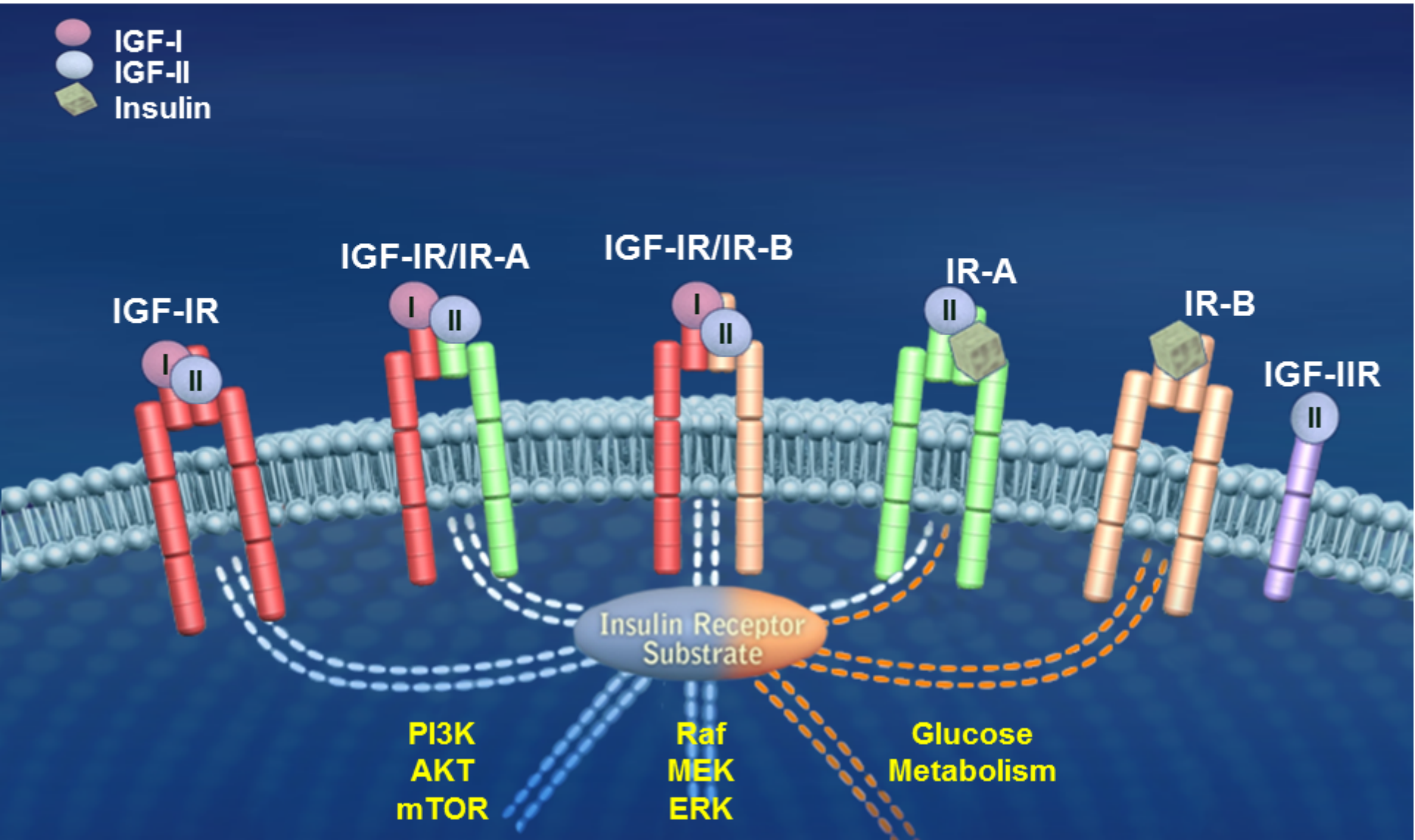
Challenges with Targeting the IGF Pathway: IGF-IR Antibodies



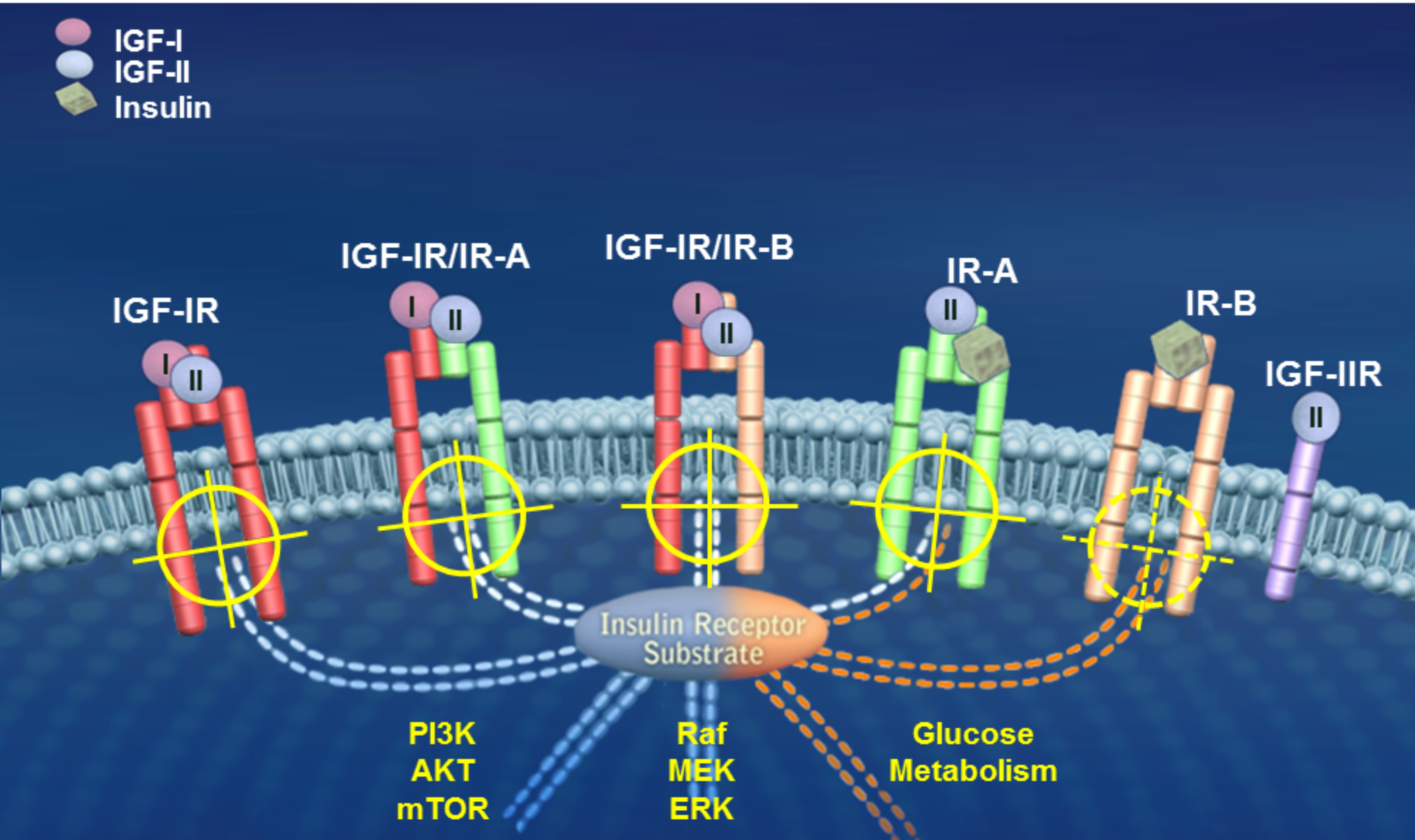
Challenges with Targeting the IGF Pathway: IGF-IR Antibodies



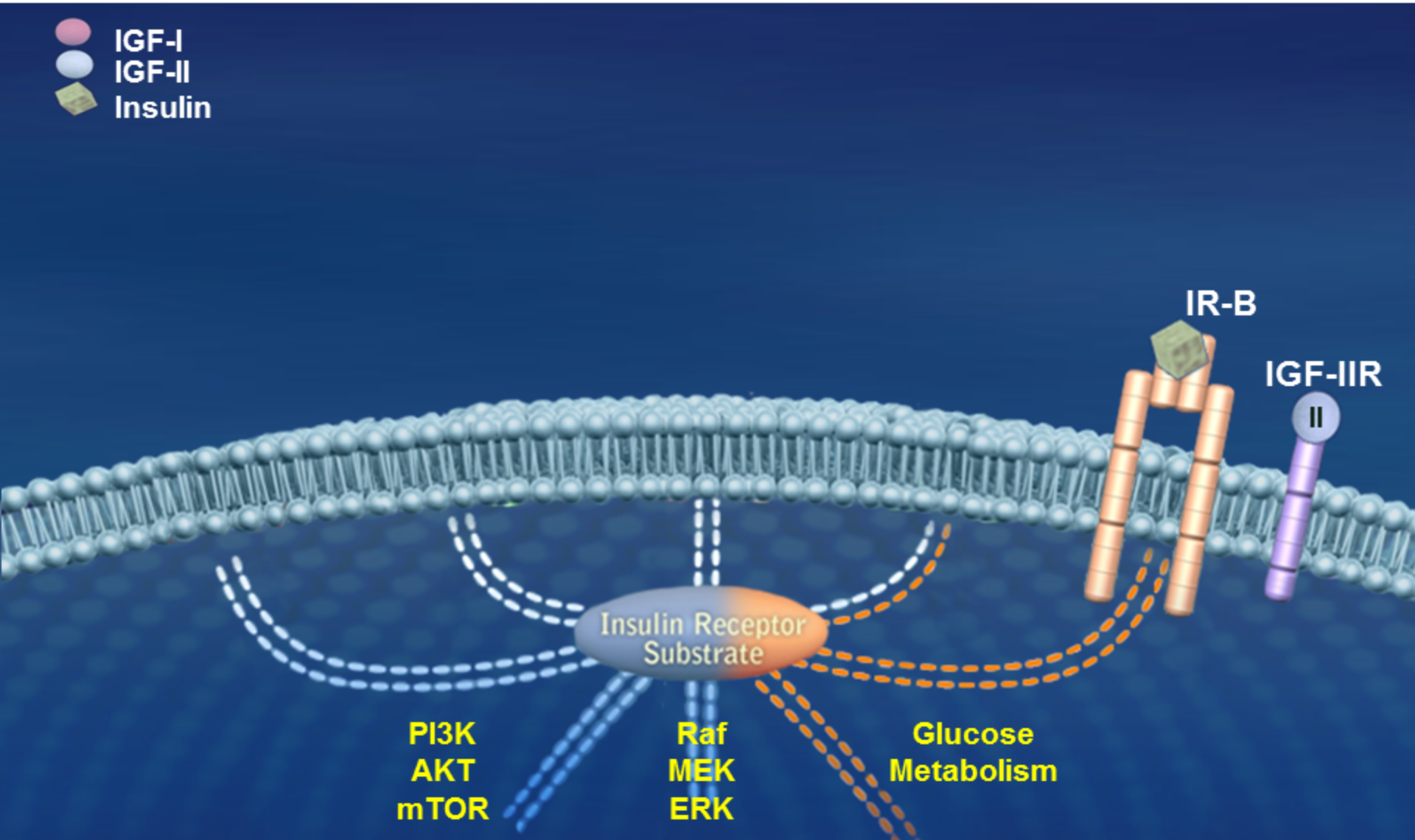
Challenges with Targeting the IGF Pathway: Small Molecules



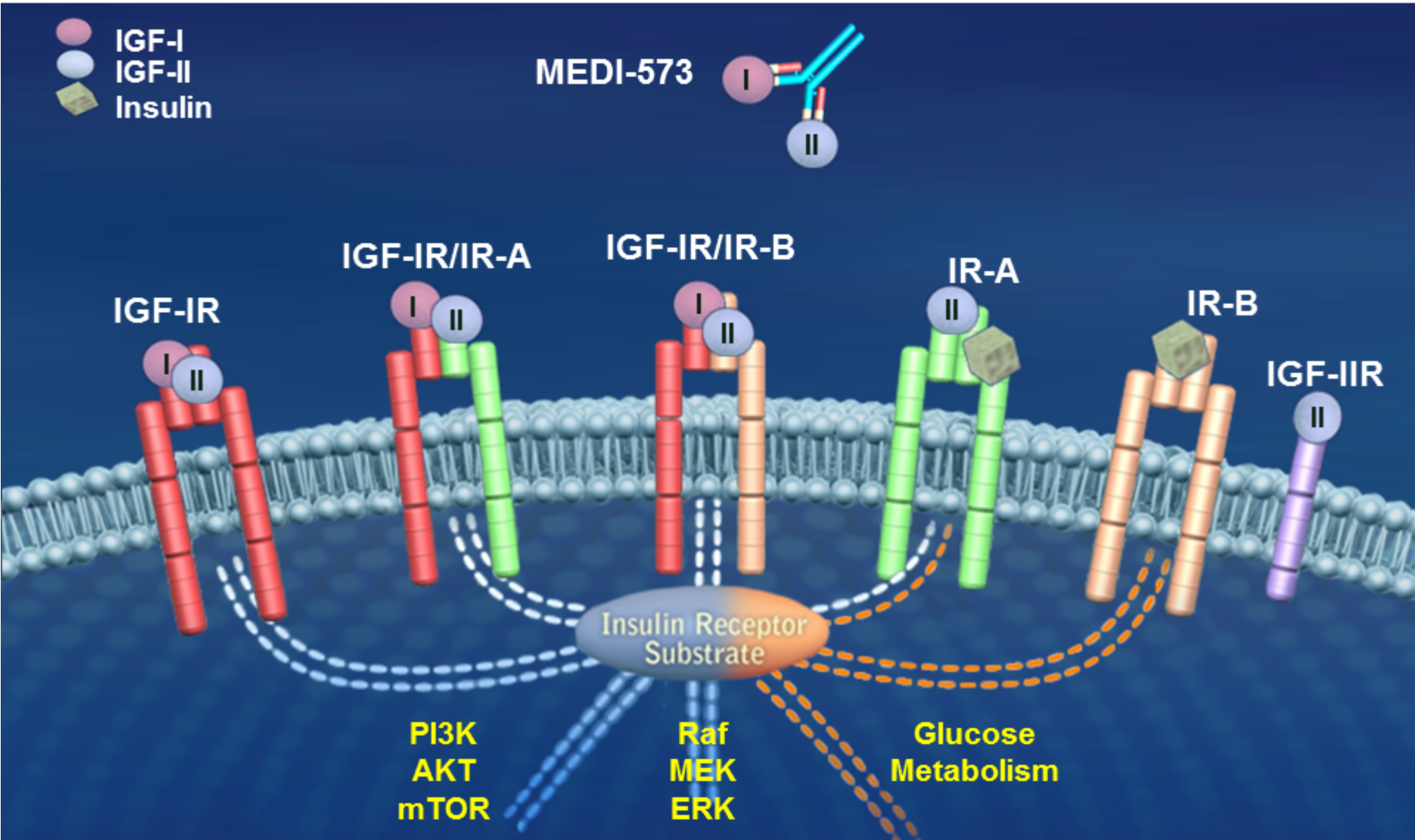
Challenges with Targeting the IGF Pathway: Small Molecules



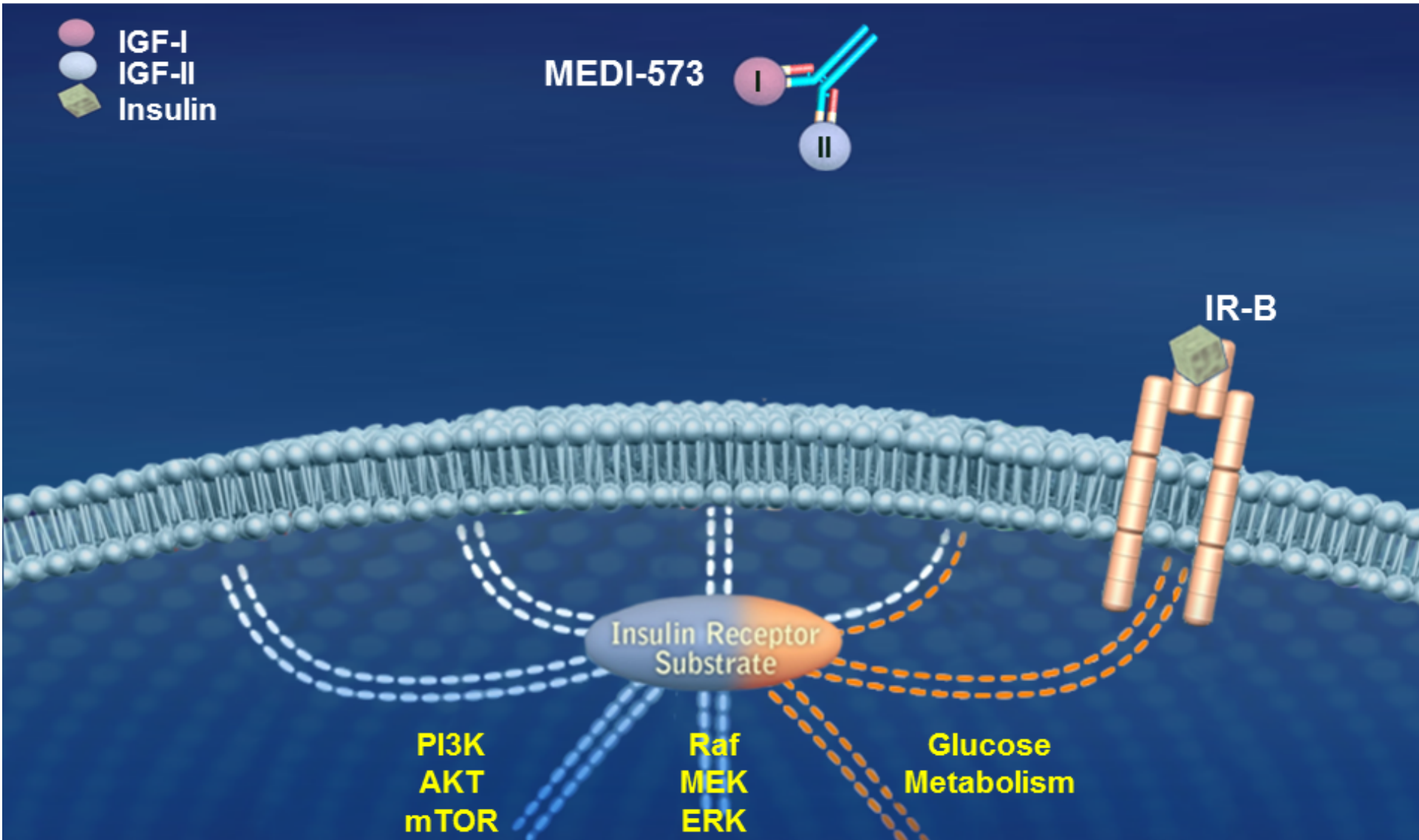
Challenges with Targeting the IGF Pathway: Small Molecules



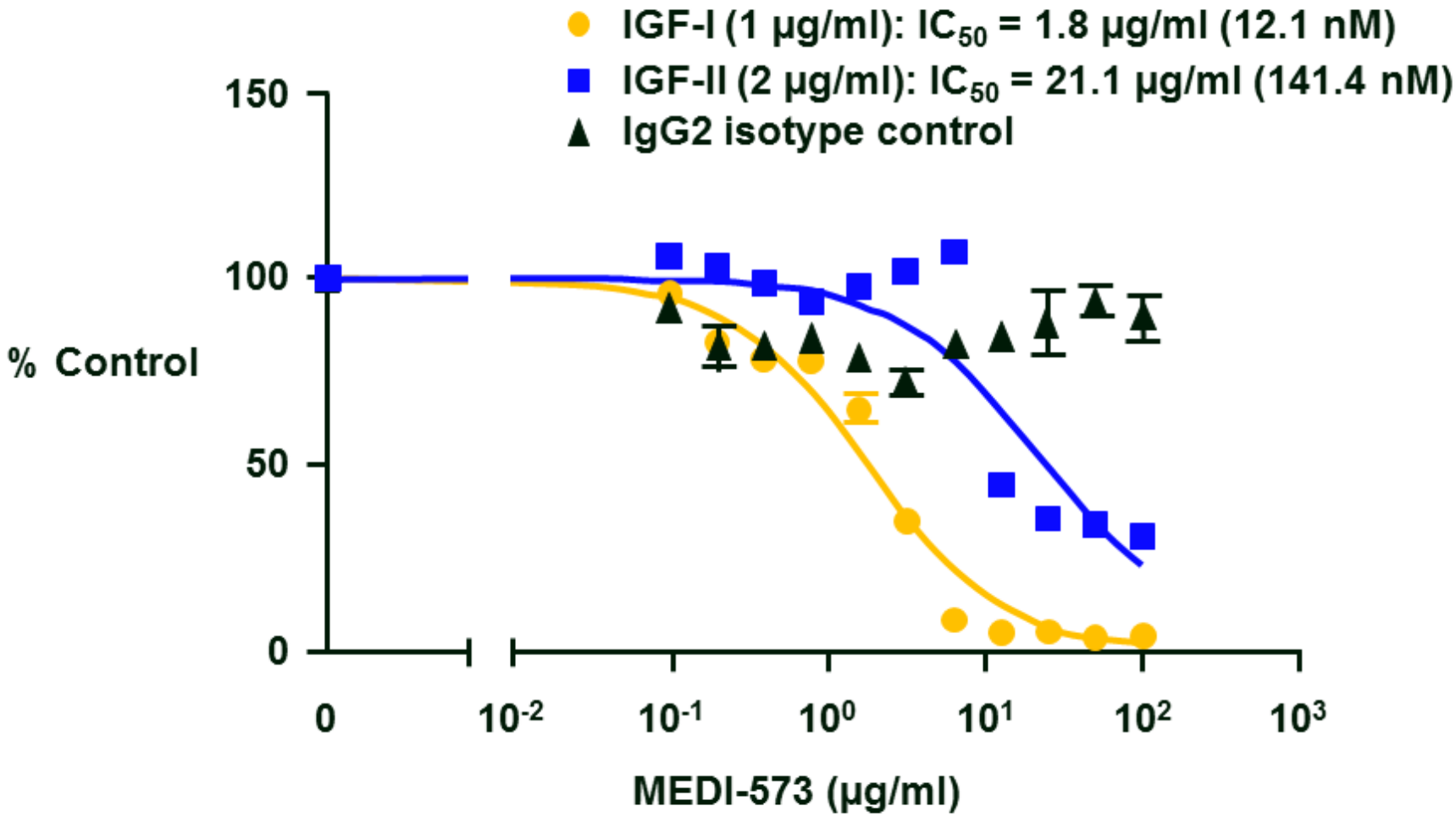
MEDI-573 Inhibits Binding of IGF-I & IGF-II Ligands



MEDI-573 Inhibits Binding of IGF-I & IGF-II Ligands



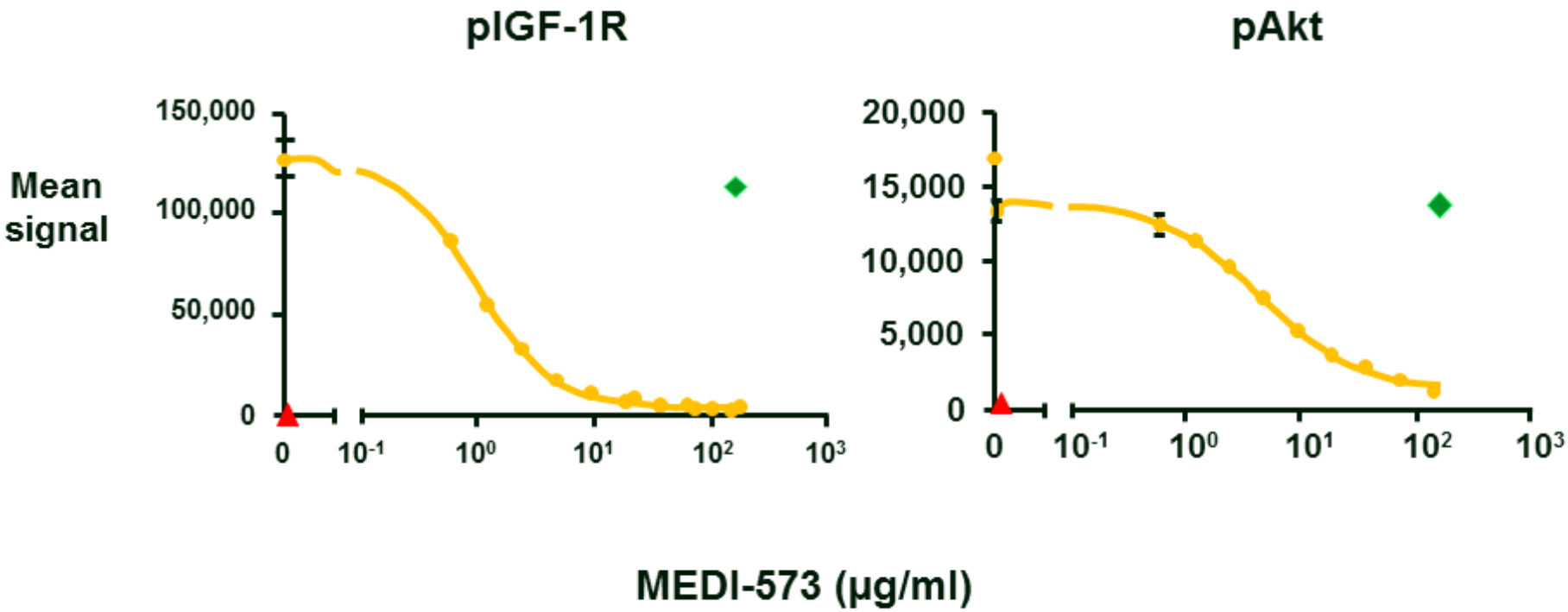
MEDI-573 Inhibits Binding of IGF-I & IGF-II Ligands to IGF-1R



J Gao et al, Cancer Res 2011

MEDI-573 Inhibits Signaling by IGF-I Ligand

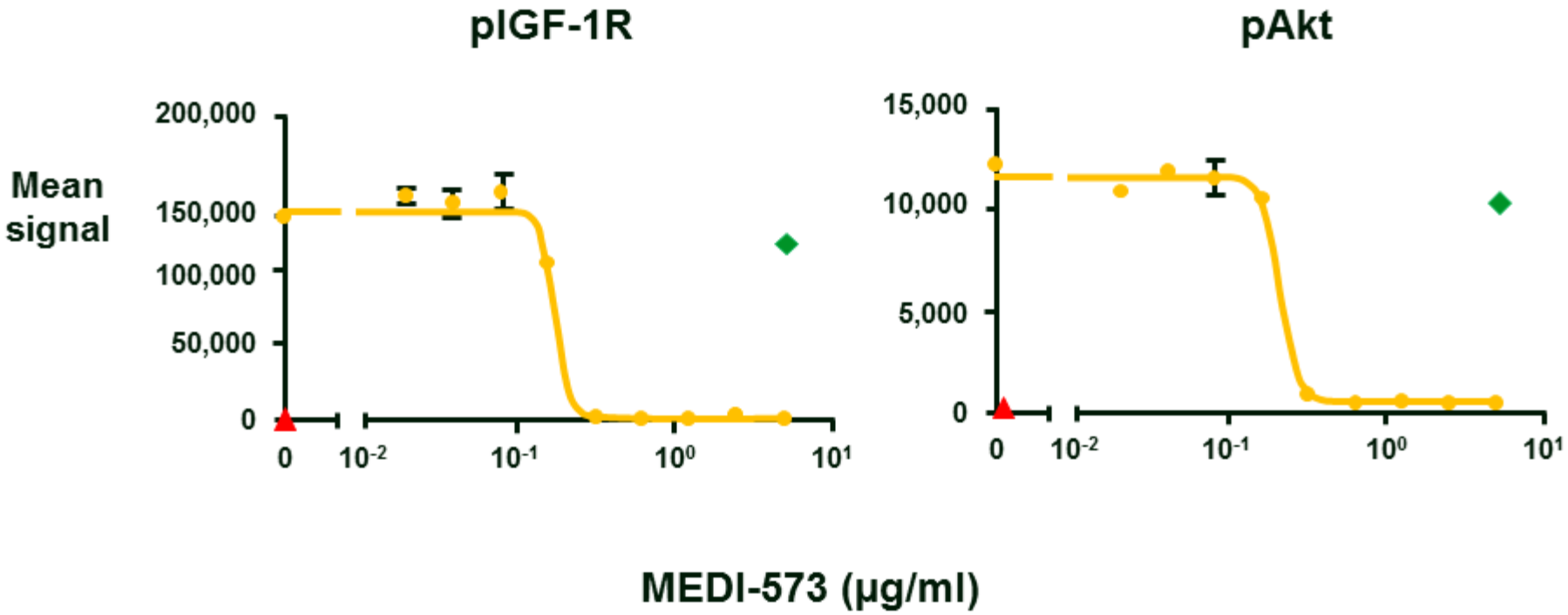
- IGF-I + MEDI-573, IC_{50} = 4.5 µg/ml (30.1 nmol/L)
- IGF-I + IgG2 (150 µg/ml)
- No IGF-1



J Gao et al, Cancer Res 2011

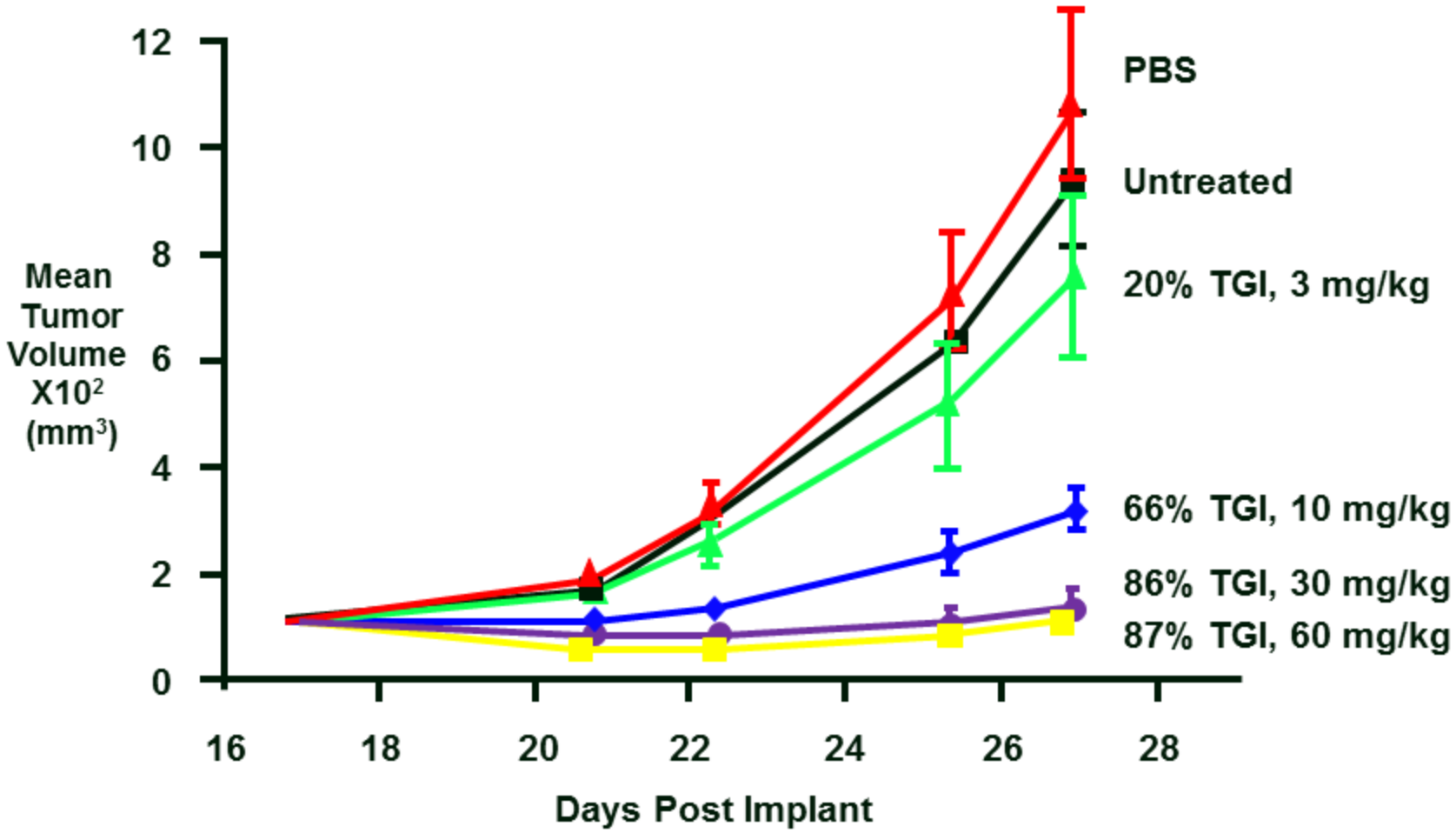
MEDI-573 Inhibits Signaling by IGF-II Ligand

- IGF-II + MEDI-573, IC_{50} = 0.2 µg/ml (1.3 nmol/L)
- IGF-II + IgG2 (5 µg/ml)
- No IGF-II



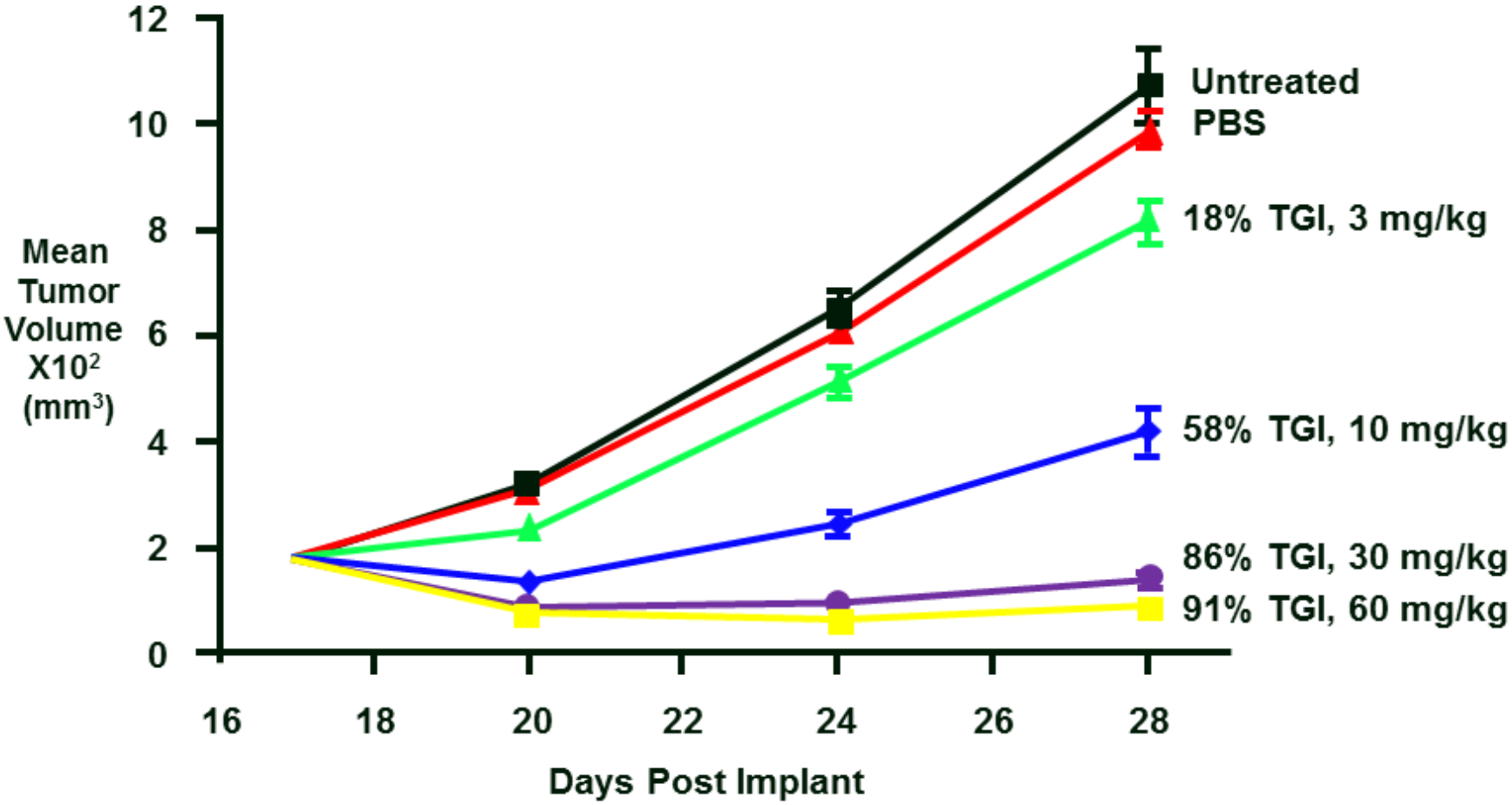
J Gao et al, Cancer Res 2011

MEDI-573 Inhibits Tumor Growth Driven by IGF-I Ligand*



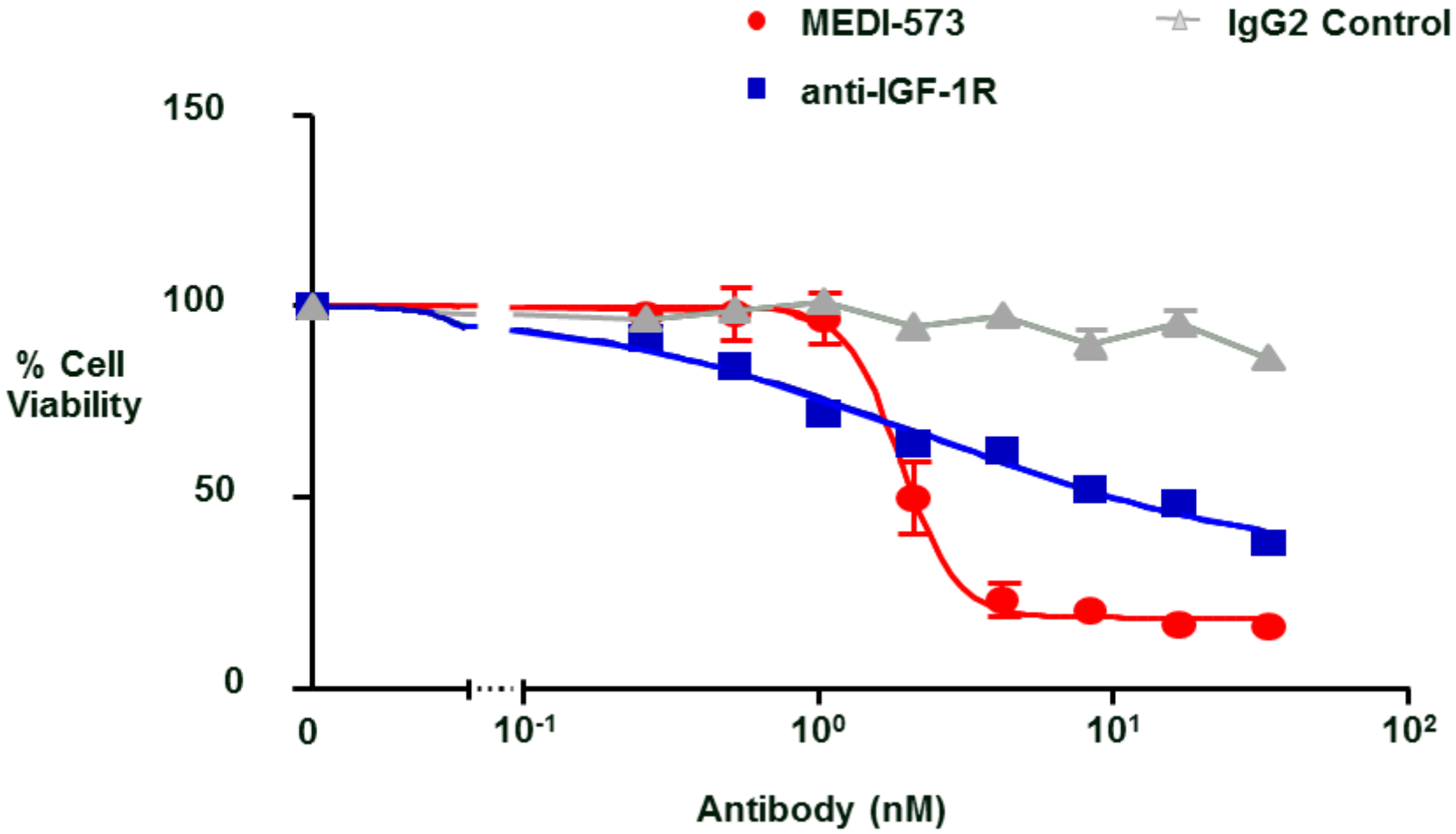
*P12 tumor growth *(in vivo)*
J Gao et al, Cancer Res 2011

MEDI-573 Inhibits Tumor Growth Driven by IGF-II Ligand*



*P12 tumor growth *(in vivo)*
J Gao et al, Cancer Res 2011

MEDI-573 Inhibits Autocrine Signaling by IGF-1R & IGF-II Ligand



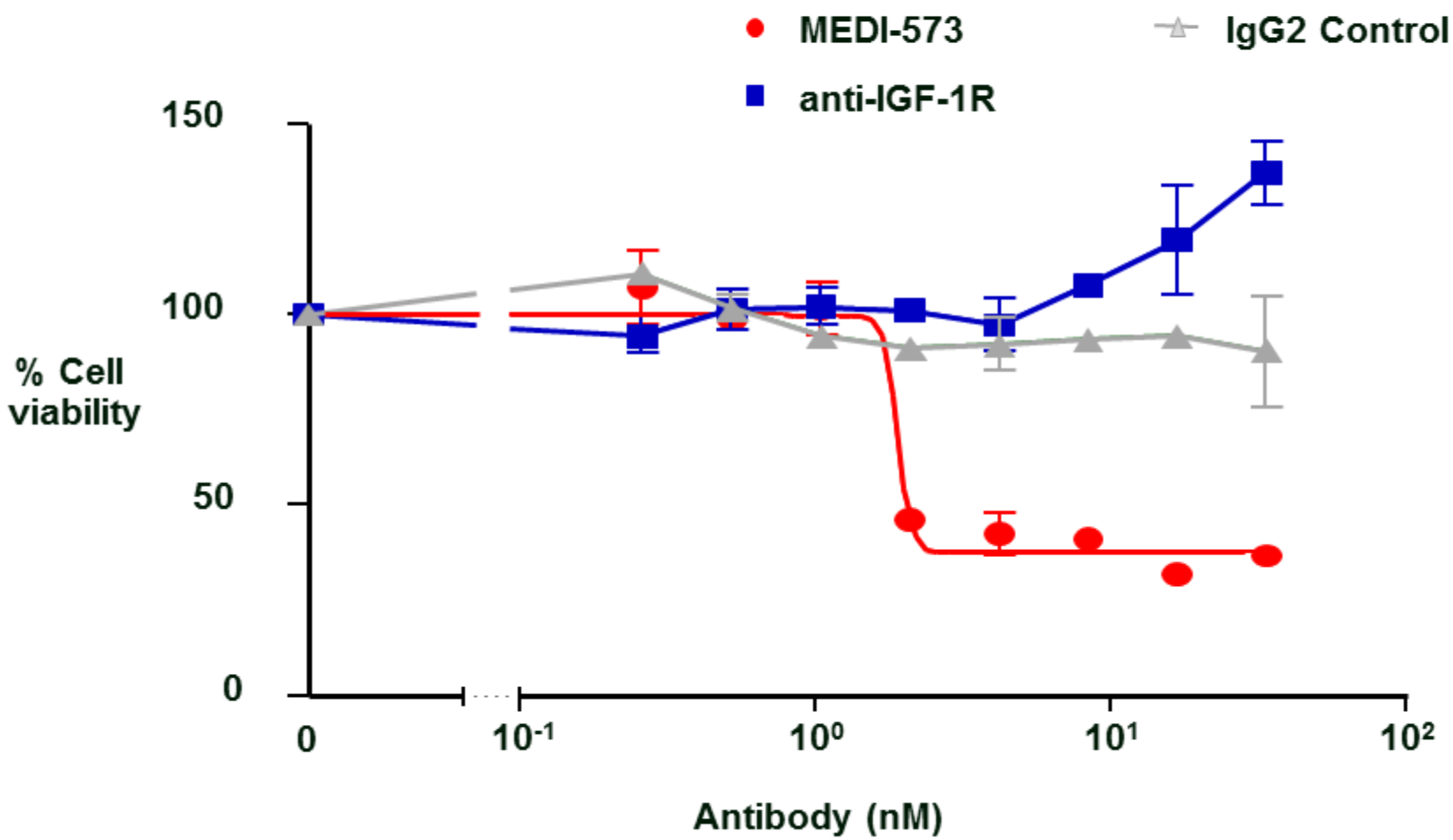
J Gao et al, Cancer Res 2011

IR-A Is Highly Expressed in Cancer Cell Lines

Cell Line	Cancer Type	IR-A %*	IR-B %
BT549	Breast	>95	<5
MDA-MB157		>95	<5
MDA – MB – 231 – KC		90	10
BT – 483		87	13
HepG2	HCC	77	23
Hep3B		73	27
T24	Bladder	70	30
UM – UC – 3		69	31
Lovo	Colorectal	67	33
J82	Bladder	65	35
MCF – 7	Breast	60	40
BT – 20		60	40
BT – 474		59	41
5637	Bladder	53	47
TCC – SUP		53	47
PLC	HCC	52	48

J Gao et al, Cancer Res 2011
*Subset of cell lines with > 50%- IR-A

MEDI-573 Inhibits Autocrine Signaling by IR-A & IGF-II Ligand



J Gao et al, Cancer Res 2011

MEDI-573 Showed No Observable Toxicity in Cynomolgus Monkeys

Group	# Doses	Dose (mg/kg)	# Animals Main (Day 92)	# Animals Recovery (Day 148)
Vehicle Control	13	0	3M/3F	2M/2F
MEDI-573		1		---
MEDI-573		10		---
MEDI-573		60		2M/2F

No changes in fasting glucose, growth hormone, or serum insulin concentrations attributed to MEDI-573 administration

MEDI-573 Clinical Trial Experience

Jaye Viner, MD, MPH

MEDI-573 FIH Trial: Dose Cohorts

Dose Cohort (mg/kg)	No. of Patients (N=37)	Schedule (IV), Duration of Infusion
0.5	4	QW, 60-min
1.5	3	
5	10*	
10	3	
15	14*	
30	3	Q3W, 90-min

* Dose expansion
Data cut-off: August 18, 2011

MEDI-573 FIH Trial: Selected Baseline Demographics

Characteristics	# of Subjects (N=37)
Age, years	
Mean (range)	61 (37–83)
Gender	
Male	21
Female	16
Prior Regimens	
Range	2–9

Haluska et al, ASCO Breast CA Symposium 2011
Data cut-off: August 18, 2011

MEDI-573 FIH Trial: Selected Eligibility Criteria

- Inclusion
  - Advanced solid tumors
  - Age ≥18 years
  - Measurable or evaluable disease
- Exclusion
  - Uncontrolled diabetes
  - Prior treatment with mAbs targeting IGF-1R

MEDI-573 FIH Trial: Tumor Types

Tumor Type	# of Subjects (N=37)
Bladder	17
Sarcoma: Leiomyosarcoma, Ewing's, Angiosarcoma, Liposarcoma	4
Colorectal	4
Prostate	3
Pancreatic	2
Esophageal	1
Breast	1
Ovarian	1
Uterine	1
Cervical	1
Adrenocortical	1
Adenocarcinoma (unknown primary)	1

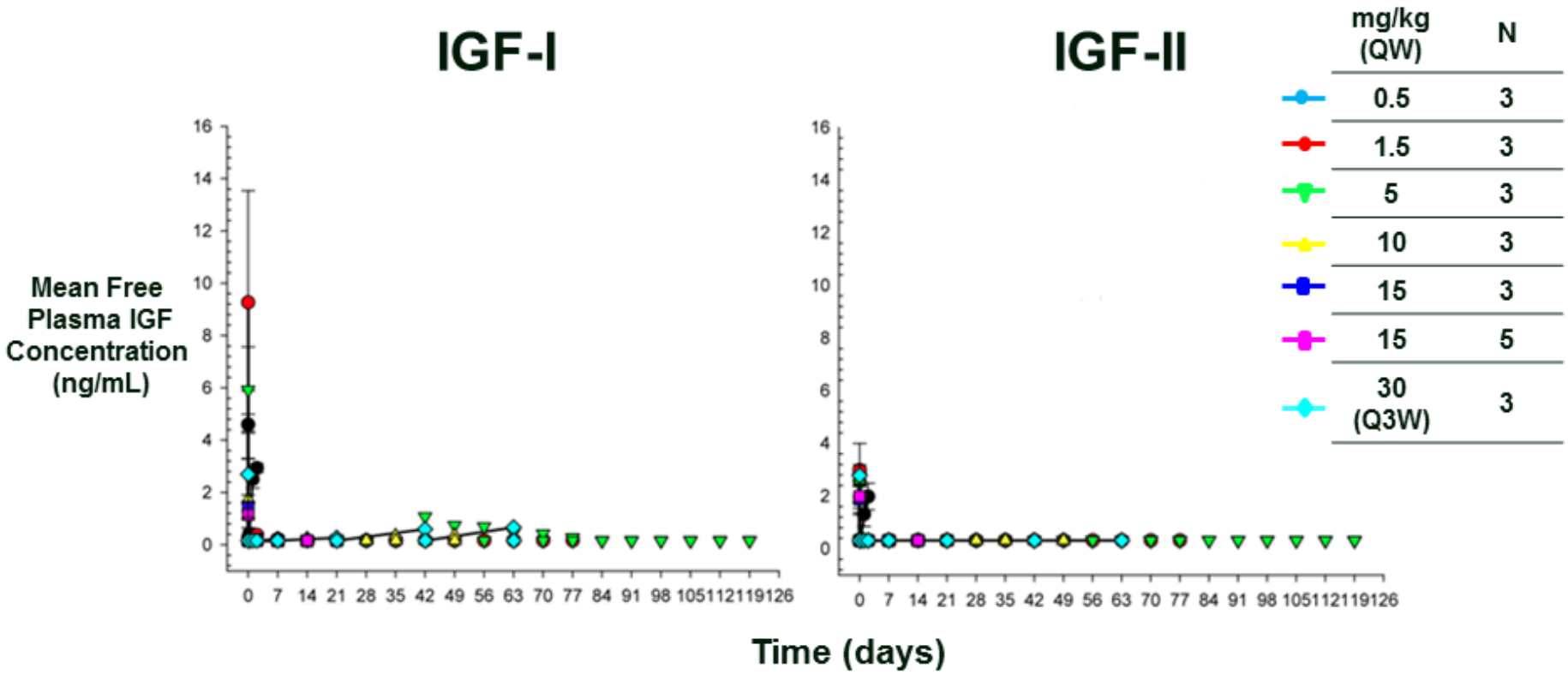
Haluska et al, ASCO Breast CA Symposium 2011; Data cut-off: August 18, 2011

MEDI-573 FIH Trial: Sarcoma Subjects' Responses to Treatment

	Diagnosis to MEDI-573 Treatment (yrs)	# Lines of Prior Therapy/ Best Response	Dose of MEDI-573	Response/ Exposure to MEDI-573 (days)
Leiomyosarcoma Stage IV	4	3/SD	5 mg/kg QW	PD (43)
Ewing's Sarcoma Stage II	5	2/PR		SD (126)
Angiosarcoma Stage IV	5	6/SD	10 mg/kg QW	SD (146)
Liposarcoma Stage IV	13	5/CR	15 mg/kg QW	SD (647)

No sarcoma subjects discontinued MEDI-573 due to toxicity

MEDI-573 FIH Trial: Suppression of IGF-I & IGF-II Ligands



Haluska et al, ASCO Breast CA Symposium 2011; Data cut-off: August 18, 2011

MEDI-573 FIH Trial: Preliminary Anti-Tumor Activity Data

Parameter	Evaluable Subjects N=27 (%)	Dose Cohort (mg/kg) 0.5 N=3	1.5 N=3	5 N=4	10 N=3	15 N=11	30* N=3
Stable Disease	11 (40.7)	0	2	3	1	3	2

- Stable disease defined as no OR or PD at 12 weeks
- No objective responses to date

*Q3W dosing; all other cohorts, QW dosing
Data cut-off: August 18, 2011

MEDI-573 FIH Trial: Summary of Serious Adverse Events

Dose (mg/kg)	Total (N=37)	SAE
0.5	2	Cancer pain; increased blood creatinine, dehydration, fatigue, decreased GFR
1.5	1	Malignant neoplasm
5	2	Infection, renal obstruction; cholangitis
10	0	n/a
15	5	Hypoglycemia*, decreased weight*, confusion, decreased appetite; urosepsis; small intestinal obstruction; hemoptysis, hypercalcemia; ureteral stent infection, acute renal failure
30 (Q3W)	0	n/a

*Treatment-related; both occurred in 1 subject

- 20 SAEs reported for 10 subjects
- 2 treatment-related SAEs reported for 1 subject (15 mg/kg QW cohort)

Haluska et al, ASCO Breast CA Symposium 2011
Data cut-off: August 18, 2011

MEDI-573 FIH Trial: Treatment-related Adverse Events Occurring in ≥10% Subjects

AE	# of Subjects Reporting AEs (N=37)	
	N	%
Decreased appetite	8	22
Fatigue	8	22
Nausea	6	16
Diarrhea	5	14
Anemia	4	11

- No AEs were grade 3, 4, or 5*
- No DLTs occurred* *
- 1 subject discontinued MEDI-573 due to AEs deemed possibly related (thrombocytopenia and anemia)

*Data cut-off: August 18, 2011
**Defined as ≥ grade 3 treatment-related AE during 1st treatment cycle
Haluska et al, ASCO Breast CA Symposium 2011

MEDI-573 FIH Trial: Hyperglycemic Adverse Events (N=2)

- Grade 1 (1 subject)
  - Not related
- Grade 3 (1 subject)
  - Remotely related

Data cut-off: August 18, 2011

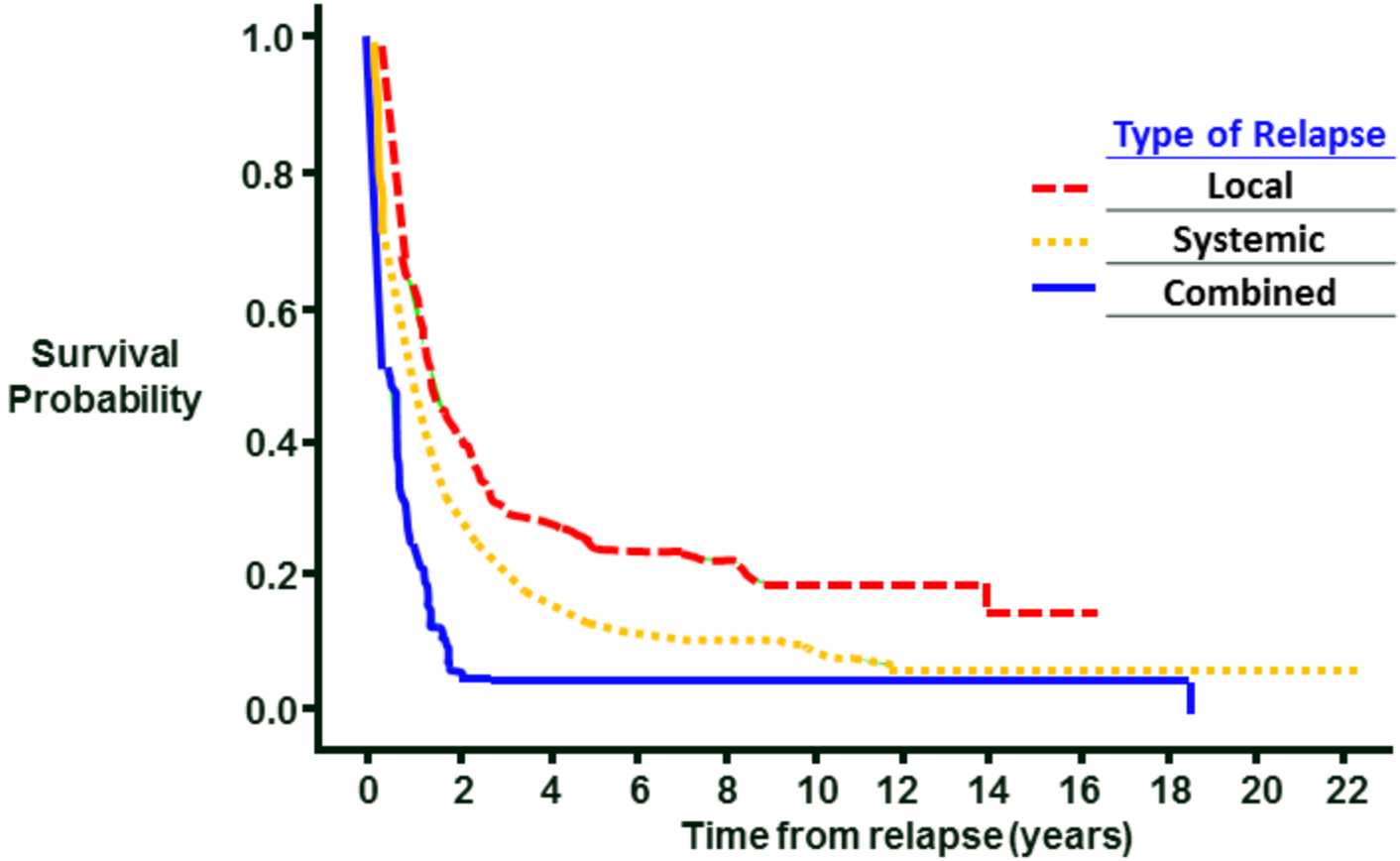
Current MEDI-573 Phase 1b/2 Trials

- Breast Cancer
  - MEDI-573 in combination with an aromatase inhibitor (AI) versus AI alone in women with metastatic breast cancer
- Hepatocellular Carcinoma
  - MEDI-573 in combination with sorafenib versus sorafenib alone in adult subjects with unresectable or metastatic hepatocellular carcinoma

MEDI-573 in Pediatric Settings & Conclusion

Robert Sikorski, MD, PhD

Ewing's Sarcoma Prognosis Is Poor after 1st Relapse



Survival after relapse according to type of relapse (N = 714; P < 0.001)
Stahl et al. Pediatr Blood Cancer 2011

Potential Initial Trial of MEDI-573 in Pediatric Sarcoma Subjects

- Trial Objective
  - Obtain safety and pharmacokinetic data in a pediatric population
- Eligibility
  - Pediatric age range
  - Refractory to standard treatments
  - Ewing's sarcoma family of tumors, osteosarcoma, or rhabdomyosarcoma

Issue 1: Ewing's Sarcoma Is Rare

United States 2010	Incidence	5-yr Prevalence
Total Sarcoma	21,262	78,006
Ewing's (all ages)	475	1,911
Ewing's (age 0-14)	166	631

SEER*Stat 7.0.4 (Incidence Rates) and US Census Population Data

Issue 2: Design of Advanced Trial

- Age of subjects
- Mixed sarcoma vs. homogenous Ewing's tumor
- Single arm vs. randomized
- Chemotherapy partner

Issue 3: Endpoints

- ORR
- PFS
- OS
- SD
- CBR
- Duration of Response

Issue 4: Clinical Benefit

- Approximately 10% ORR achieved with IGF targeting monotherapy in Ewing's sarcoma

Conclusion

- IGF-targeting agents show modest activity in sarcoma
- MEDI-573 is novel, targets ligands
- Challenges for advanced clinical development in pediatric settings