



The Insulin-like growth factors as targets for the treatment of sarcoma

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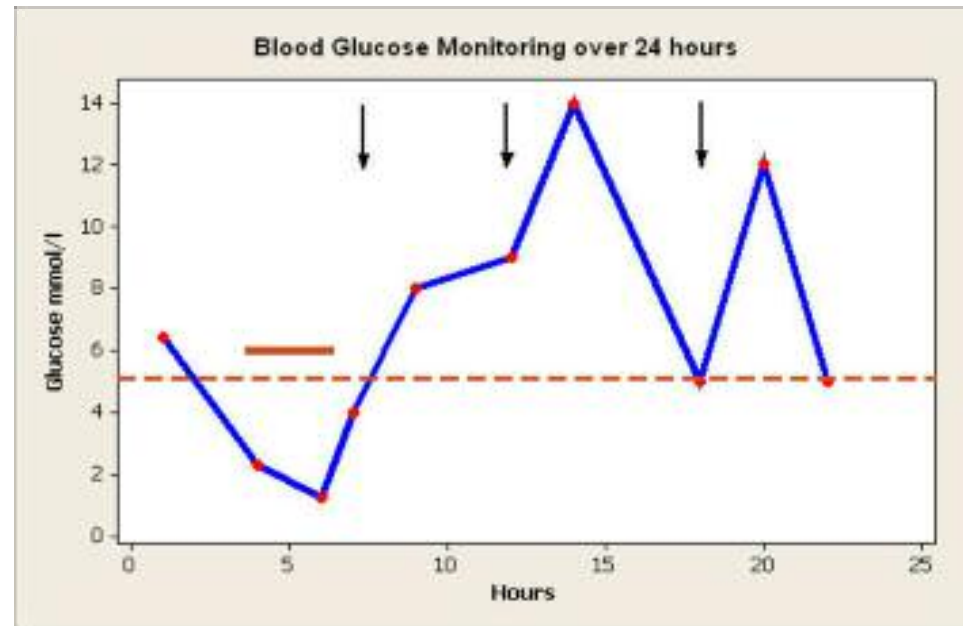

Oxford Sarcoma

Male Age 50

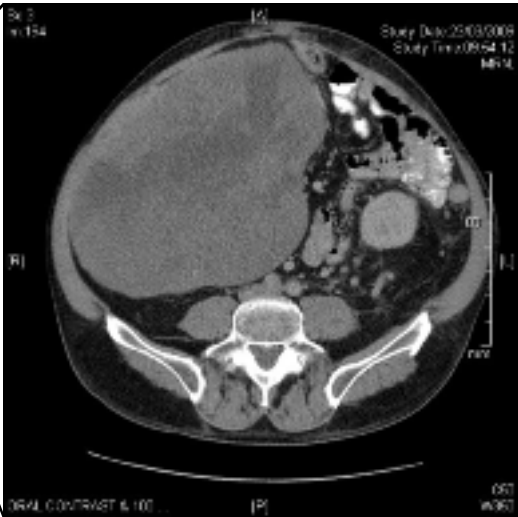
Early morning aggression and confusion

Abdominal distension

Skin thickening



CT scan

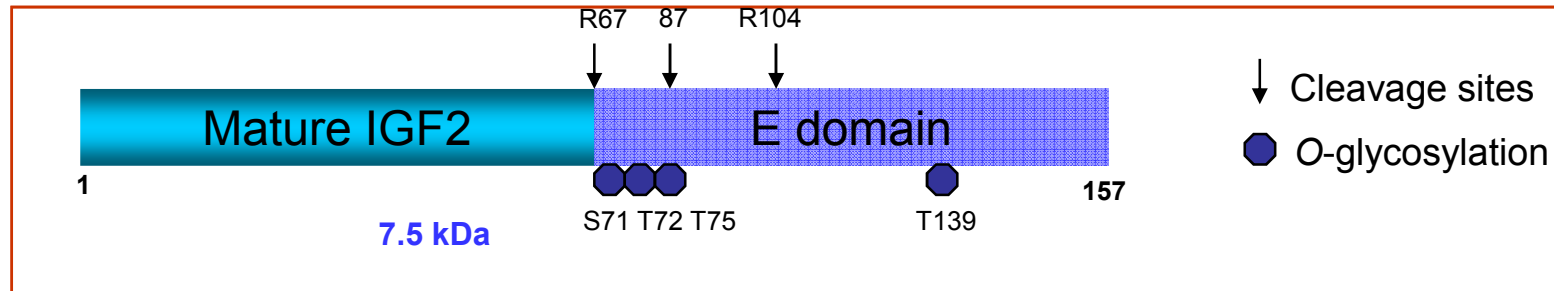


IGF2 = 53ng/ml
NR (IGF2Big) < 18ng/ml

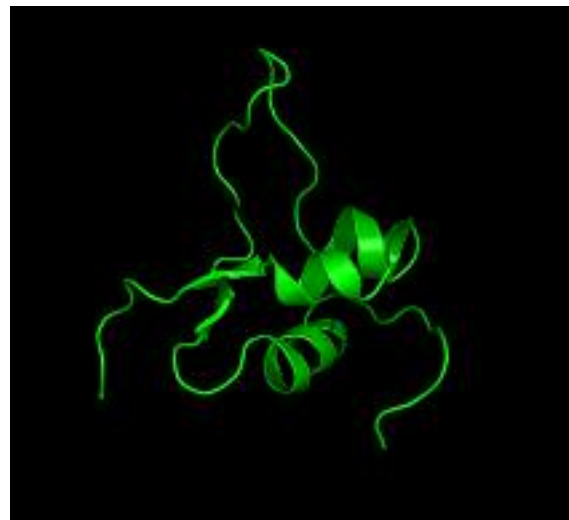
Diagnosis
Solitary Fibrous Tumour (Haemangiopericytoma)



Insulin-like growth factor 2



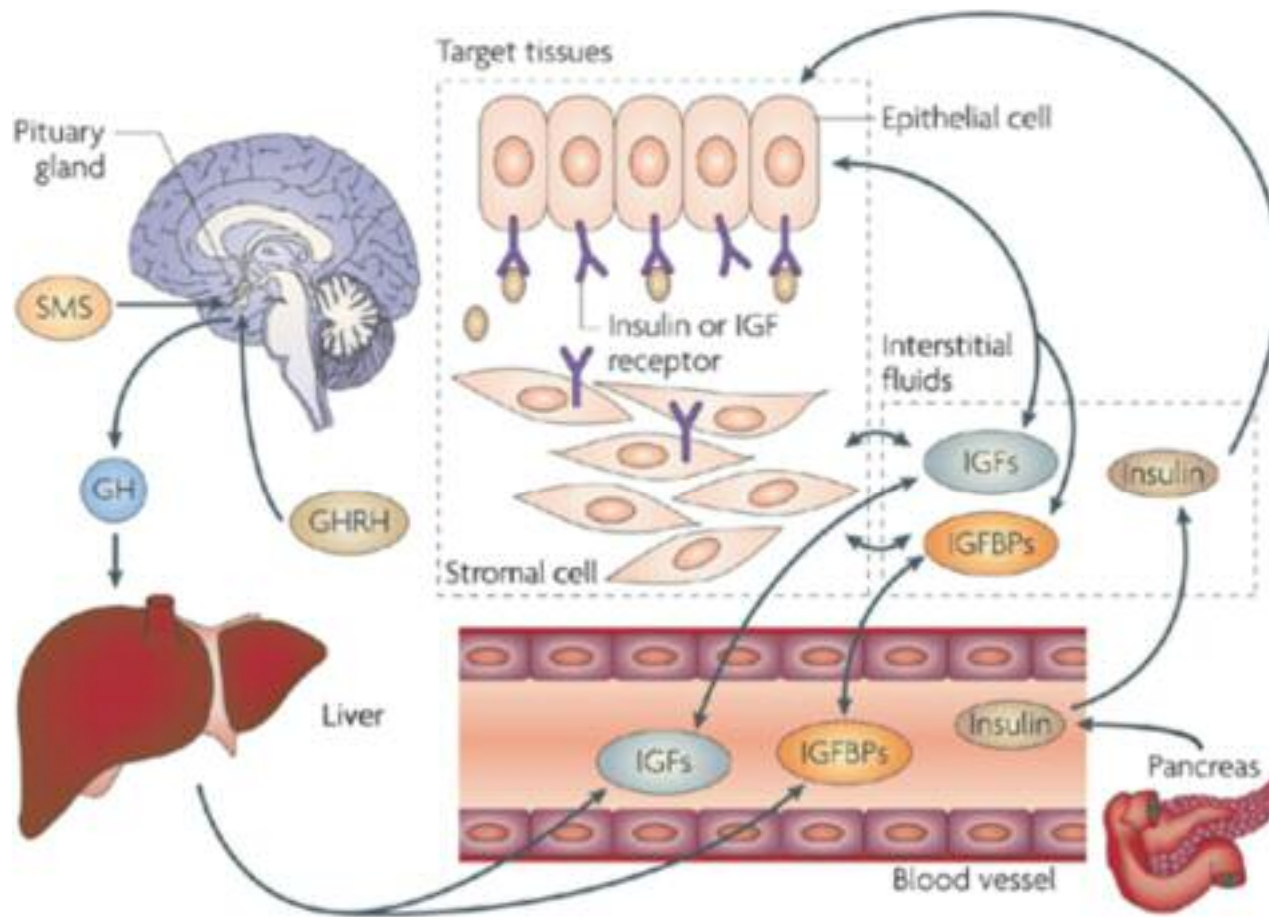
	34	15 16	24	31	49 50 51	60	
IGF-I	1 --GP- E TLCG A ELVD A L Q FVCGDRGF Y F NK P TGYGSS SRR APQT GIV D ECCFRSCDL RR LE M Y CA PLK PAKS A	70					
IGF-II	1 AYRP S ETLCG G ELVD T L Q FVCGDRGF Y F SR P ASR -- V SRR S -- R GIV E ECCFRSCDL A L LE T Y CA ---T PAKS E	67					
	6	26 27	43	48 49 50	54 55	59	
Insulin a1	23	19	6 8 11	23 24 25			
	GIVEQCCTSICSLYQLENYCN - FVNQHLCGSHLVEALYLVCGERGFFYTDKT		b30				
	α-chain		β-chain				



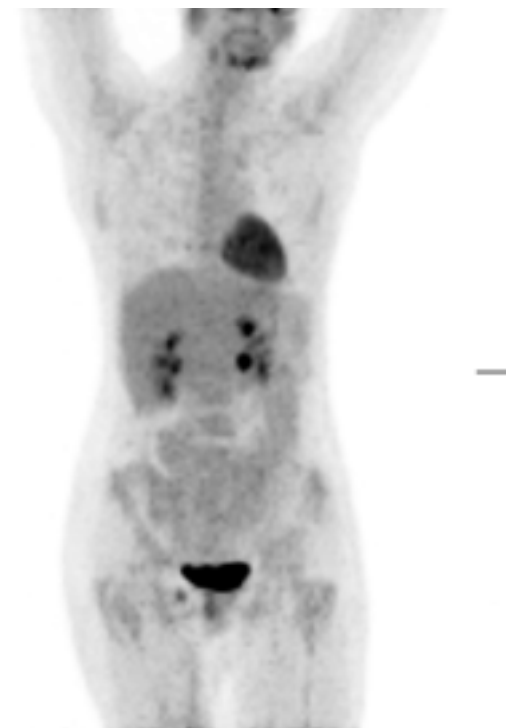
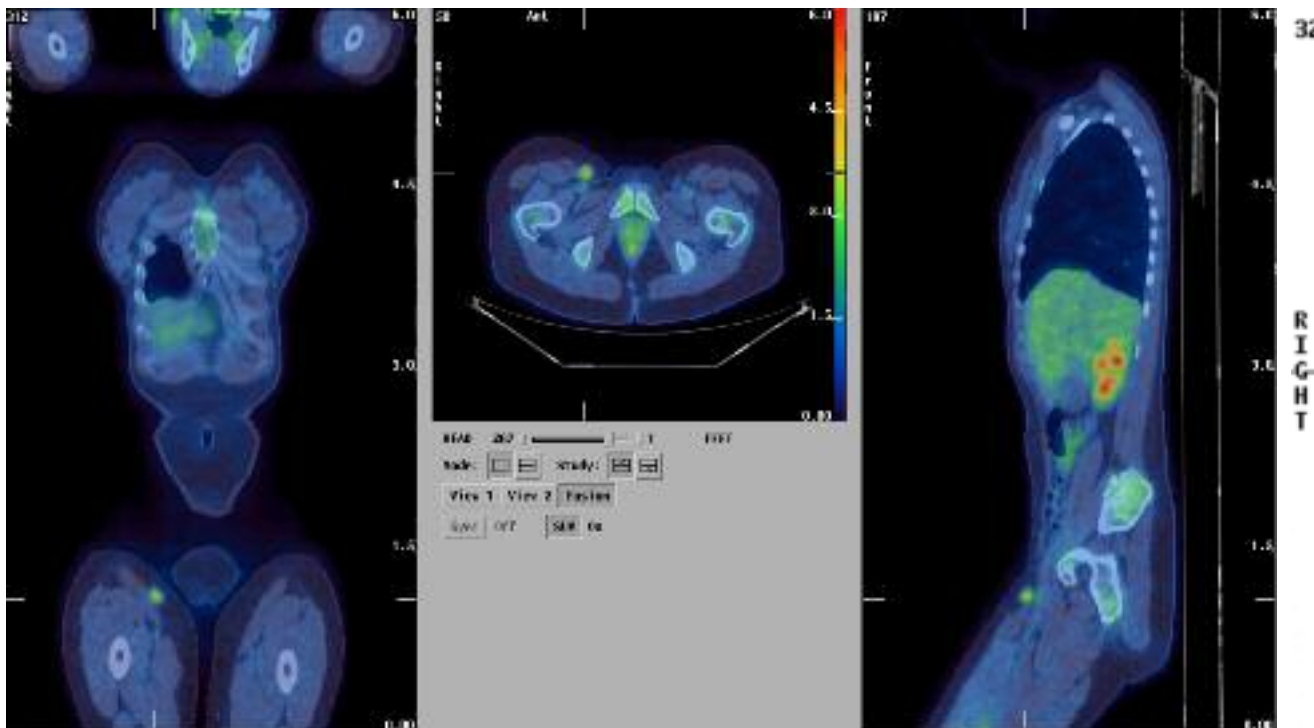
Hassan BSG Feb 2010



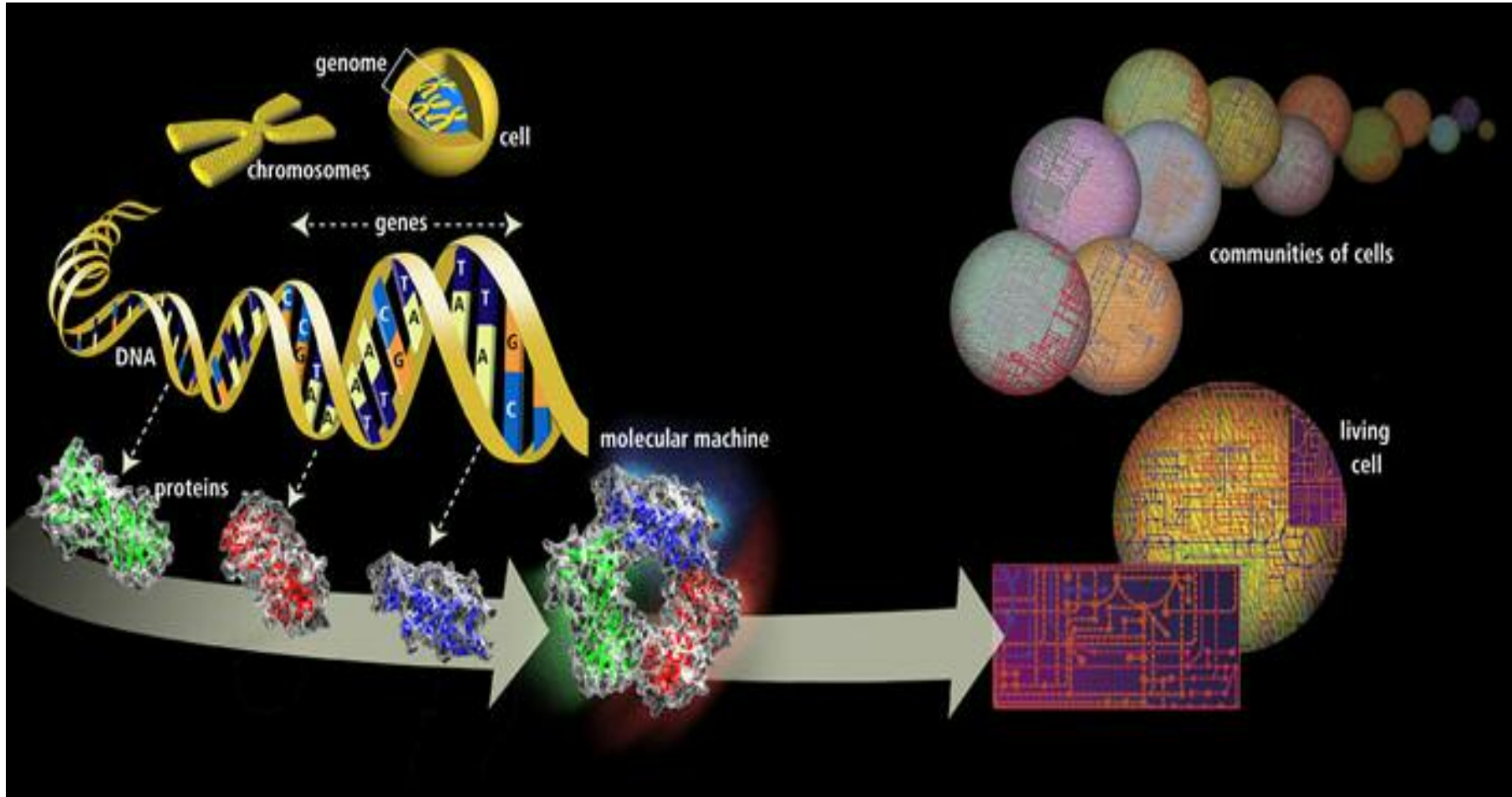
Insulin-like Growth Factors- Endocrine, Paracrine, Autocrine



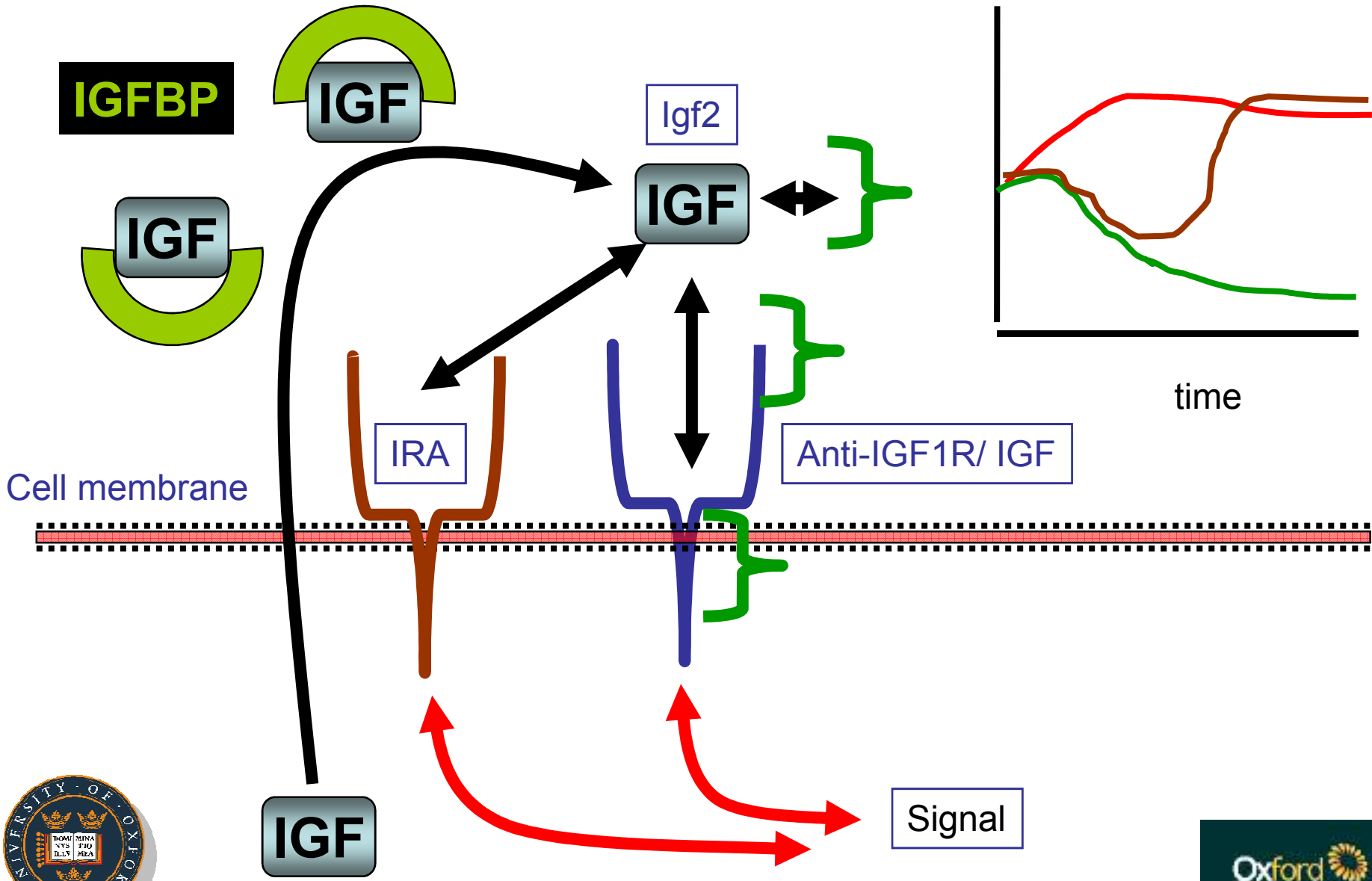
PET (glucose) scan



Life and Sarcoma



Sarcoma Growth Switch





Loss of function

Decreased Expression
Protease cleavage

Ewing^{EWS-FLI1}
Osteosarcoma^{p53}



Gain of function

Loss of imprinting (LOI)
Increased expression

Synovial Sarcoma^{SS18-SSX1/2}
Emb^{UPD} Alveo^{PAX3-FKHR}
Rhabdomyosarcoma
Osteosarcoma
Solitary Fibrous Tumour
Chondrosarcoma
Leiomyosarcoma



Gain of function

Increased Expression
Kinase Mutation

DSCRT^{EWS-WT1}
Kit^{WT} GIST



Strategies for Targeting the IGF pathway



Recombinant IGFBP3

Protease cleavage mutations
IGF independent activity



Humanised anti-IGF1R Antibodies
Small Molecule Kinase Inhibitors

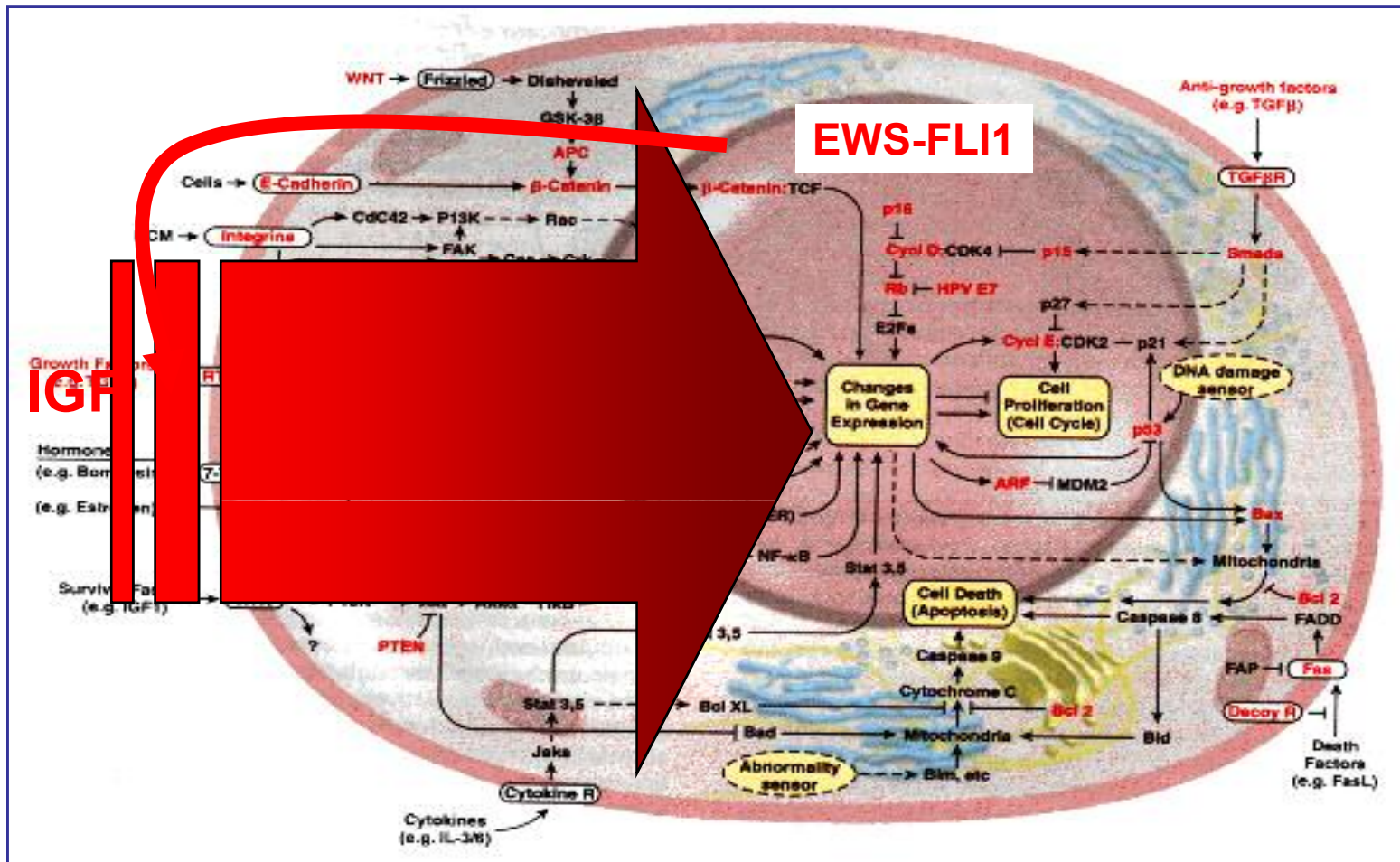
IRA resistance



Humanised anti-IGF2 Antibodies
Soluble Recombinant IGF2R

IGF2 specific

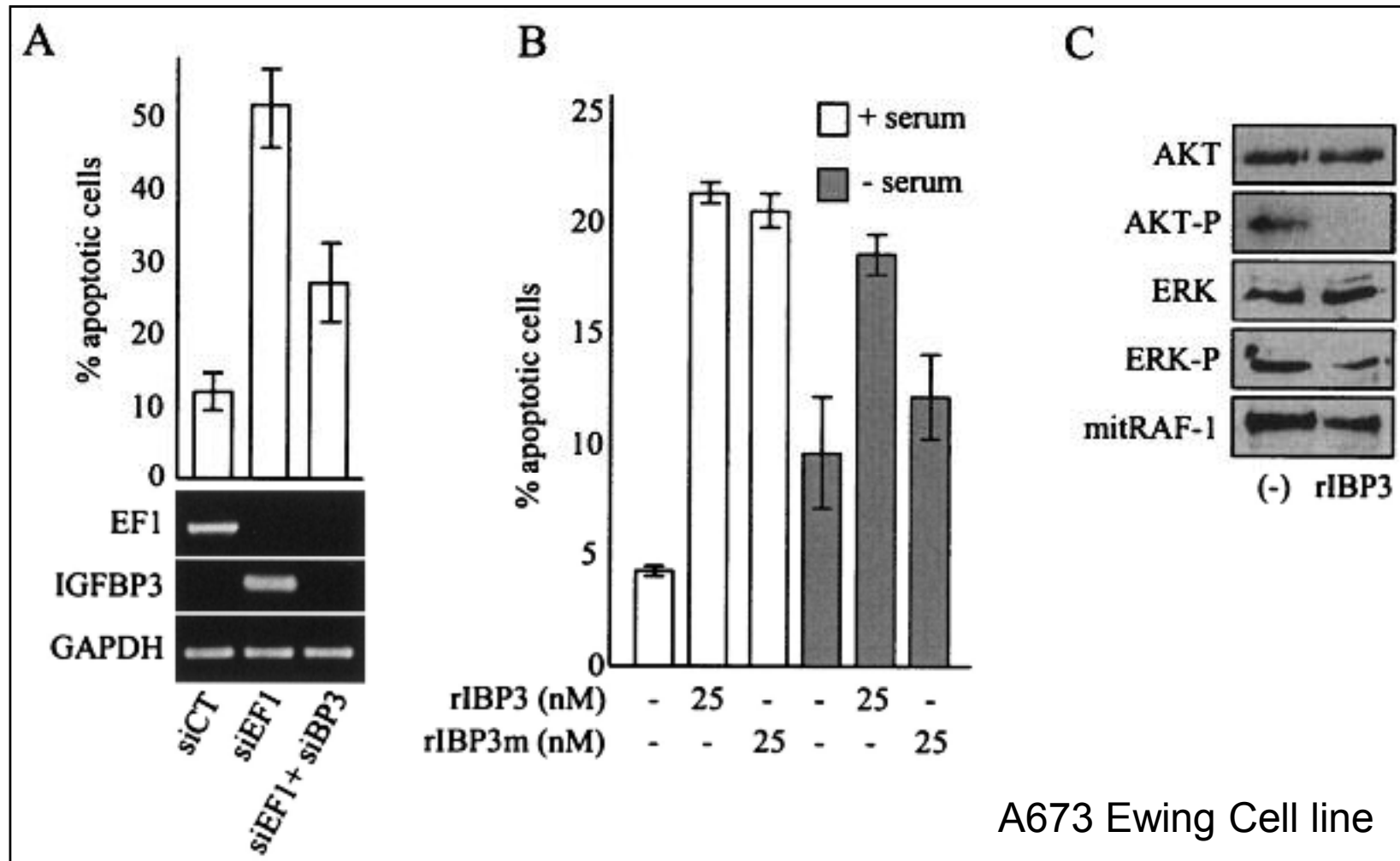




Hannahan and Weinberg 2000



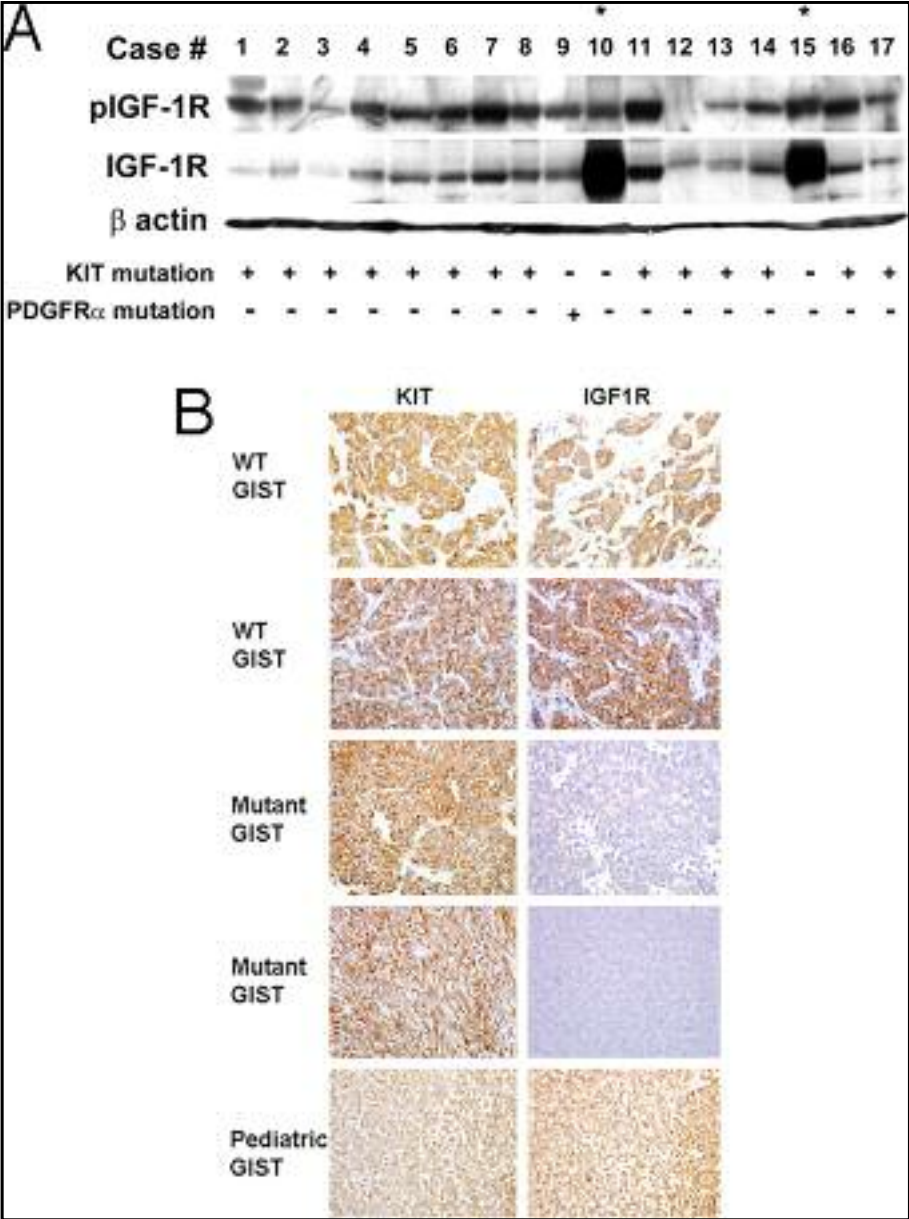
IGFBP3 in Ewing Sarcoma



Priour et al 2004 Mol Cell Biol 24; 7275-7283



IGF1R expression in GIST biopsies



Tarn C et al. PNAS
2008;105:8387-8392



Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study

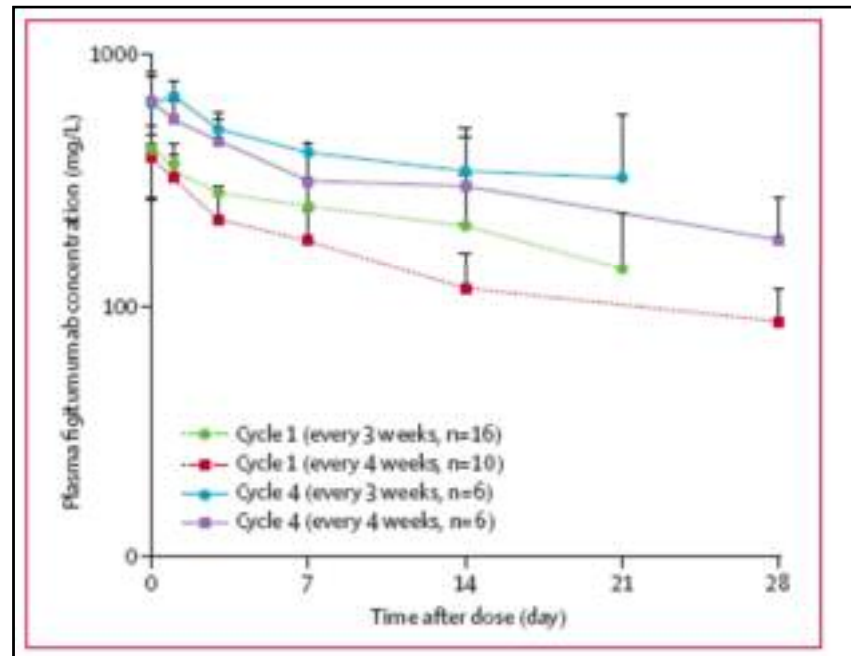
2009 Lancet Oncology

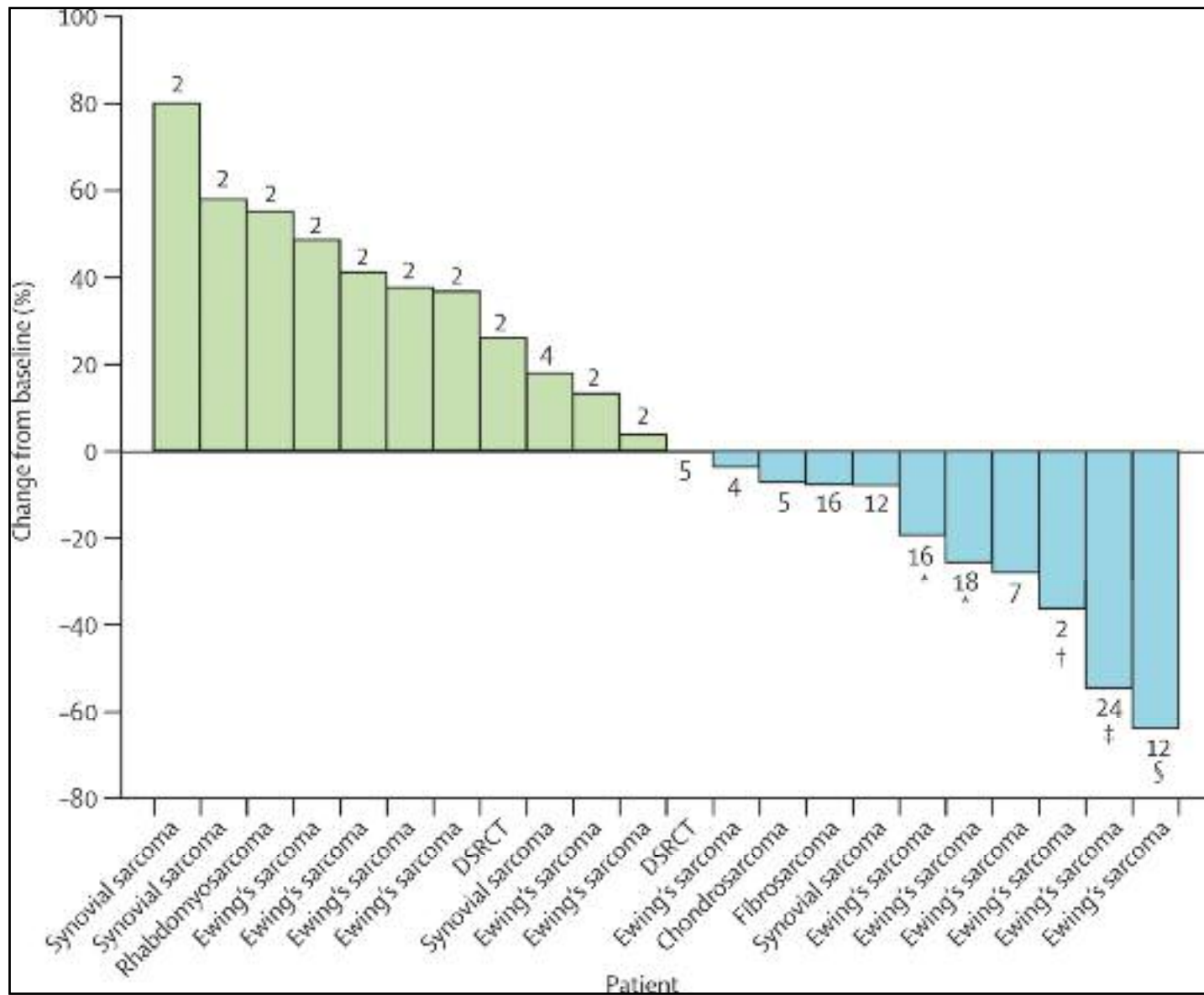
David Olmos, Sophie Postel-Vinay, L Rhoda Mofife, Scott H Okuno, Scott M Schuetz, M Luisa Paccagnello, Gretchen N Batzel, Donghua Yin, Kathryn Pritchard-Jones, Ian Judson, Francis P Worden, Antonio Gualberto, Michele Saur, Johann S de Bono, Paul Haluska

	Grade 2	Grade 3	Grade 4	Total (%)
Deep venous thrombosis	–	1	–	3.5
Anorexia/decreased appetite	2	–	–	6.9
Arthralgia	2	–	–	6.9
Diarrhoea	2	–	–	6.9
Back pain	1	1	–	6.9
Fatigue	3	–	–	10.4
Headache	3	–	–	10.4
Limb cramps	2	–	–	6.9
Skin reactions (rash/urticaria/ infection/eczema)	4	–	–	13.7
Candidiasis (oral or vaginal)	2	–	–	6.9
Vomiting	1	1	–	6.9
Weight loss	2	–	–	6.9
Laboratory abnormalities				
Raised uric acid concentration	–	–	1	3.5
Raised ALT concentration	–	–	1*	3.5
Raised AST concentration	–	1*	–	3.5
Anaemia/low haemoglobin	2	–	–	6.9
Raised GGT concentration	2	1*	–	10.4
Lymphocyte count decrease	2	–	–	6.9

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=gamma-glutamyltransferase. *Grade 3 raised GGT and AST concentrations, and grade 4 ALT, were reported in the same patient; these adverse events were initially attributed to figitumumab, but resolved upon discontinuation of concomitant paracetamol, fluconazole, and lorazepam.

Table 2: Number of adverse events of grade 2 or higher attributed to figitumumab (N=29)





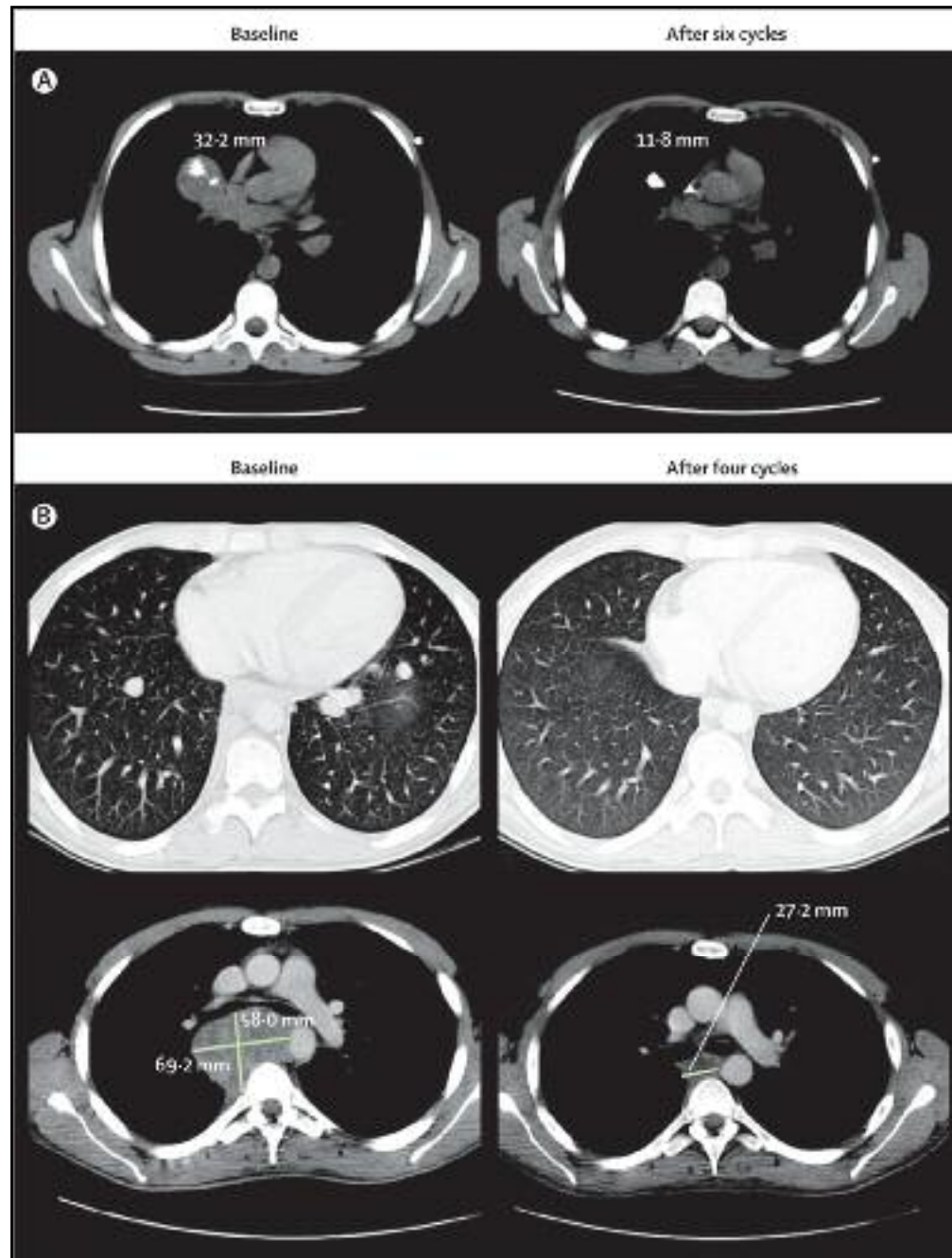


Table 2 Compounds in clinical development that target the insulin-like growth factor 1 receptor.

Type of agent	Compound	Company	IC ₅₀	Development phase of testing	Type of tumors targeted	Efficacy in combination and reference
Antibody IgG2	CP-751,871 ⁵⁰	Pfizer	1.8 nM IGF1 binding	Phase I	MM	Adriamycin, 5-FU ⁵⁰
Antibody	EM164 ^{37,38} / AVE1642 ³⁹	ImmunoGen/ Sanofi-Aventis	K _d : 0.1 nM	Preclinical— <i>in vitro, in vivo</i>	90 <i>in vitro</i> and 27 <i>in vivo</i> cell lines	Gemcitabine ³⁷
Antibody	IMC-A12 ⁴¹	ImClone	1 nM IGF1 binding	Phase I	Clinical solid tumors	C225 ⁴⁰
Antibody	R1507	Roche	NA	Phase I	Solid tumors <i>in vivo</i> Colo205, NCI-H322M	NR
Antibody	AMG479	Amgen	K _d = 0.3 nM	Phase I	<i>In vivo</i> Colo-205, BxPC-3, MiaPaCa	Gemcitabine, irinotecan
Antibody	19D12	Schering	NA	Preclinical— <i>in vitro, in vivo</i>	NSCLC, ovarian A2780	NR
Antibody	h7C10 ⁴⁹	Pierre Fabre/Merck	4.2 nM IGF-1 binding	Preclinical— <i>in vitro, in vivo</i>	MCF-7, A549 etc.	Navelbine, C225 ⁴⁹
TK inhibitor non-ATP	PPP ^{44–47}	Karolinska Institute	<0.05 μM	Preclinical— <i>in vitro, in vivo</i>	MM, uveal melanoma	NR
TK inhibitor	AG 538 AG1024	Hebrew University of Jerusalem	IC ₅₀ = 61 nM	Preclinical— <i>in vitro, in vivo</i>	Breast, prostate leukemia etc.	NR
TK inhibitor	Compound-1	OSI Pharmaceuticals	19 nM	Preclinical— <i>in vitro, in vivo</i>	NSCLC colorectal	Erlotinib
TK inhibitor	NVP-ADW742 ^{42,100}	Novartis	0.17 μM	Preclinical— <i>in vitro, in vivo</i>	MM ⁴² , SCLC cell lines ¹⁰⁰	Imatinib, ⁸² etoposide, carboplatin ¹⁰⁰
TK inhibitor	NVP-AEW541 ^{43,99,101}	Novartis	0.086 μM	Preclinical— <i>in vitro, in vivo</i>	Sarcoma, NET	Vincristine, ifostamide ¹⁰¹
TK inhibitor	BMS-554417 ⁴⁸	Bristol-Myers Squibb	67.9 nM	Preclinical— <i>in vitro, in vivo</i>	Leukemia, breast and ovarian cancer	NR
TK inhibitor	BMS-536924 ¹⁰²	Bristol-Myers Squibb	100 nM	Preclinical— <i>in vitro, in vivo</i>	Prostate, colon, pancreatic	NR

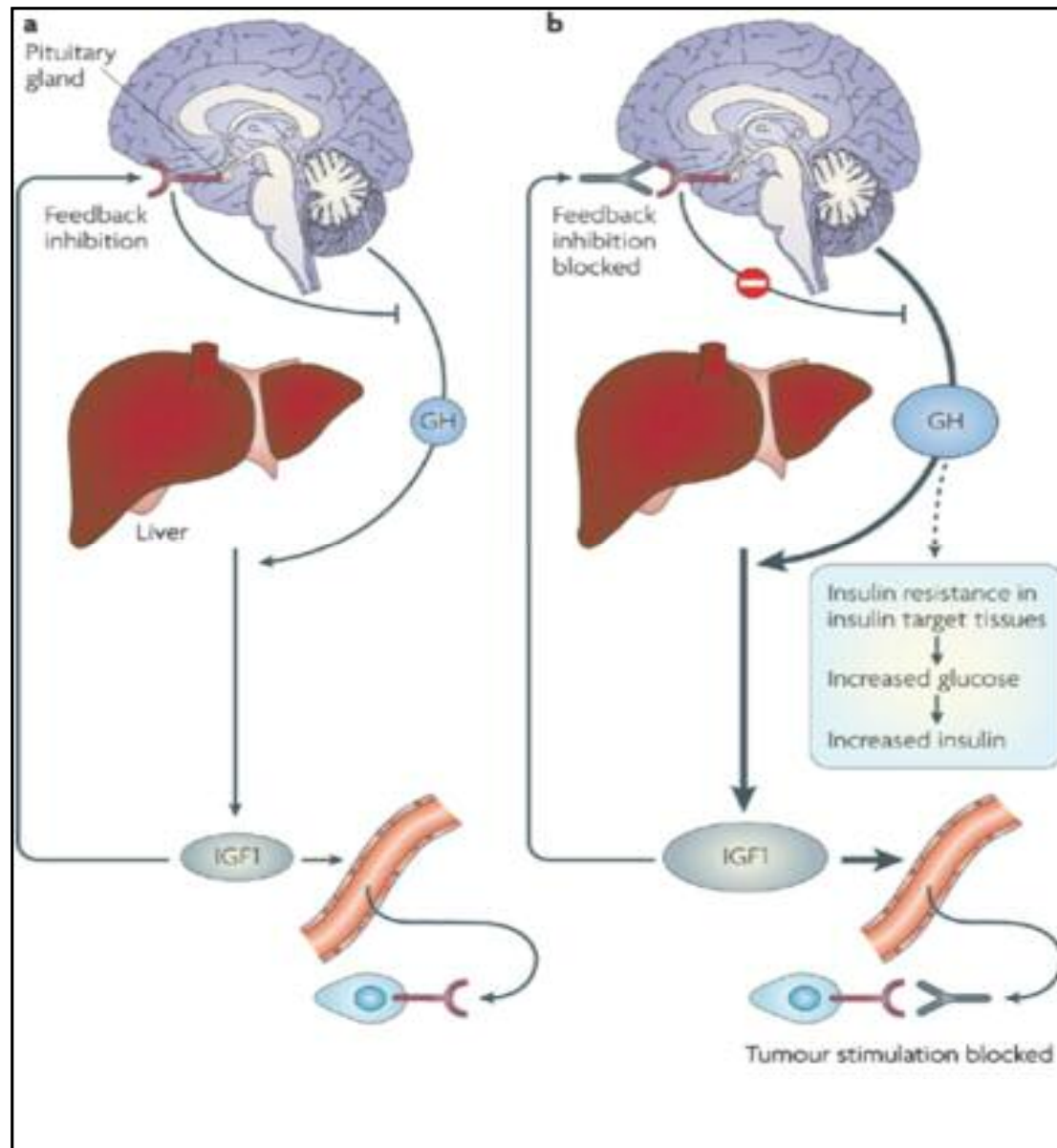
Abbreviations: FU, fluorouracil; IGF, insulin-like growth factor; MM, multiple myeloma; NET, neuroendocrine tumors; NA, data not available; NR, data not reported; NSCLC, non-small-cell lung cancer; PPP, piropodophyllin; SCLC, small-cell lung cancer; TK, tyrosine kinase.



**Tao Y *et al.* (2007) Mechanisms of Disease: signaling of the insulin-like growth factor 1 receptor pathway—therapeutic perspectives in cancer
Nat Clin Pract Oncol 4: 591–602**



Endocrine Feedback after IGF1R inhibition



Anti- IGF1R antibody targeting in sarcoma

Well tolerated

No evidence of severe
Glycaemia derangement

Feedback effects on IGF1

No immediate cardiac or growth
effects

Resistance through **IRA**
activation

Combinations with other drugs

Longer term effects

Adjuvant treatments

More studies in sarcoma



News

12/22/2009

Roche/Genentech decide to halt development of their IGF-1R antibody

SARC recently was informed of the Roche/Genentech decision to discontinue the development of their IGF-1R antibody they now call RG-1507. Understandably, we are disappointed. At our most recent meeting with Roche they agreed that the management decision was not based upon the very preliminary unscheduled look at data from SARC 011. We believe that this drug has shown important clinical benefit and are encouraging Roche to continue the development of this antibody through an alternative mechanism. Our SARC-011 clinical trial has not been completed. We have informed our sites to continue to follow the protocol for patients actively receiving treatment and for those in follow-up. Roche has assured us that patients on treatment will continue to receive study drug. We are working out logistics for the study completion/closure. We want to thank those who have participated in this trial. We remain committed to understanding better the role of IGF-1R blockade in the treatment of sarcoma. SARC 011 has taught us as a community many important lessons. It will also provide important new clinical insight to better serve our patients in the future.



Thank you



