



Activation of the IGF-I receptor: beyond mitogenicity

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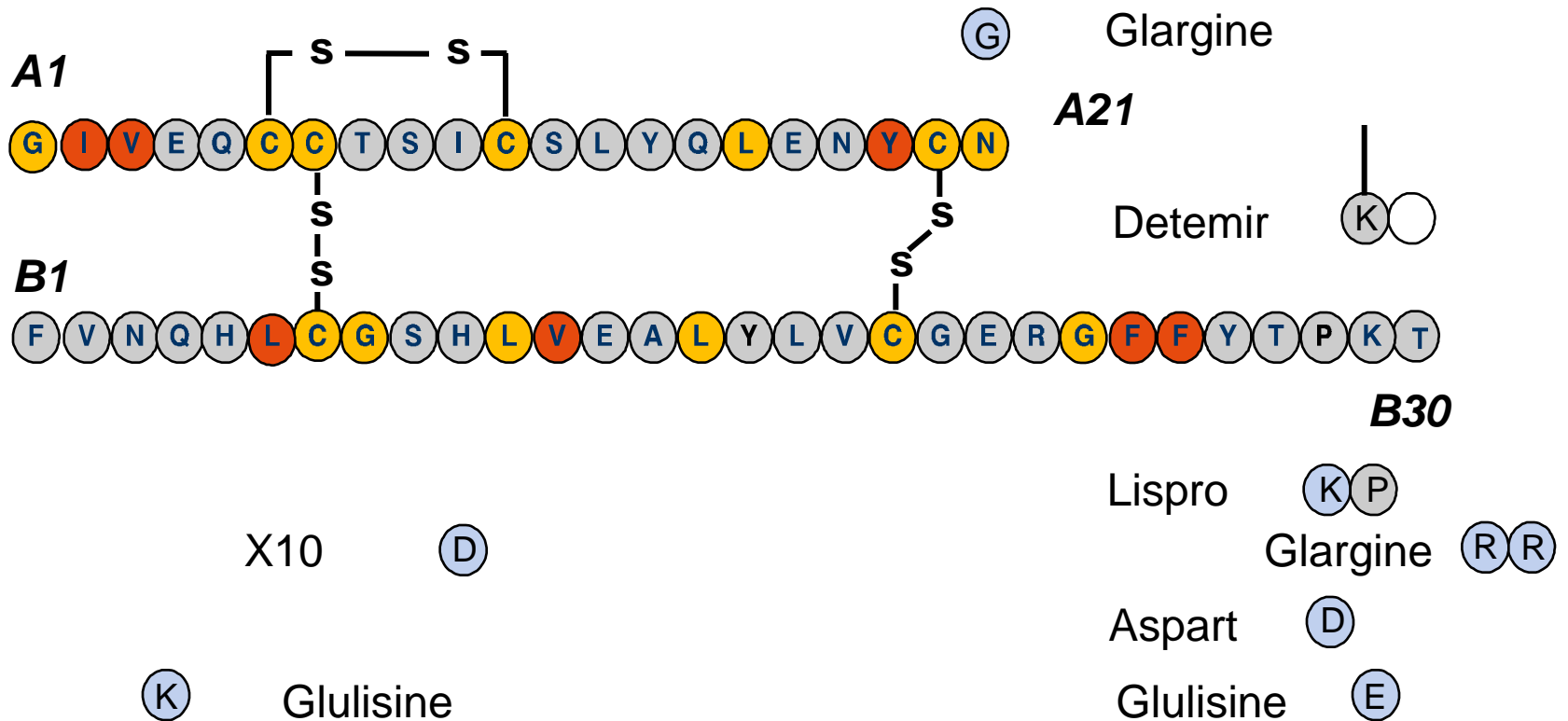
Clinical and Experimental Pharmacology Group, PICR

School of Cancer and Enabling Sciences, University of Manchester





Why interest in IGF-I



Kaarsholm & Ludvigsen. Receptor 1995;5:1–8

Pires & Chacra. Arq Bras Endocrinol Metabol 2008;52:268–78



3 messages

- Circulating total IGF-I, & to a less extent, IGFBP-3, are associated with cancer risk
- IGF-I in cancer biology is complex & goes beyond mitogenicity
- Linking diabetes (obesity) and cancer through the insulin-IGF axis – many caveats



Overall message

Epidemiological & biological observations of IGF-I & insulin in cancer biology make it plausible that 'there is a case to be answered' for insulin analogues in patients with diabetes



IGF axis and cancer epidemiology





Circulating IGF-I & cancer risk

www.sciencemag.org • SCIENCE • VOL. 279 • 23 JANUARY 1998

Plasma Insulin-Like Growth Factor-I and Prostate Cancer Risk: A Prospective Study

June M. Chan,* Meir J. Stampfer, Edward Giovannucci,
Peter H. Gann, Jing Ma, Peter Wilkinson,
Charles H. Hennekens, Michael Pollak

Initial hypothesis

Total IGF-I (mitogenic & anti-apoptotic) positively associated with cancer risk;

IGFBP-3 (pro-apoptotic) negatively associated with cancer risk.



IGF-I & cancer risk: meta-analysis

ARTICLES

Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis

Andrew G Renehan. Marcel Zwahlen. Christoph Minder. Sarah T O'Dwver. Stephen M Shalet. Matthias Egger

1346

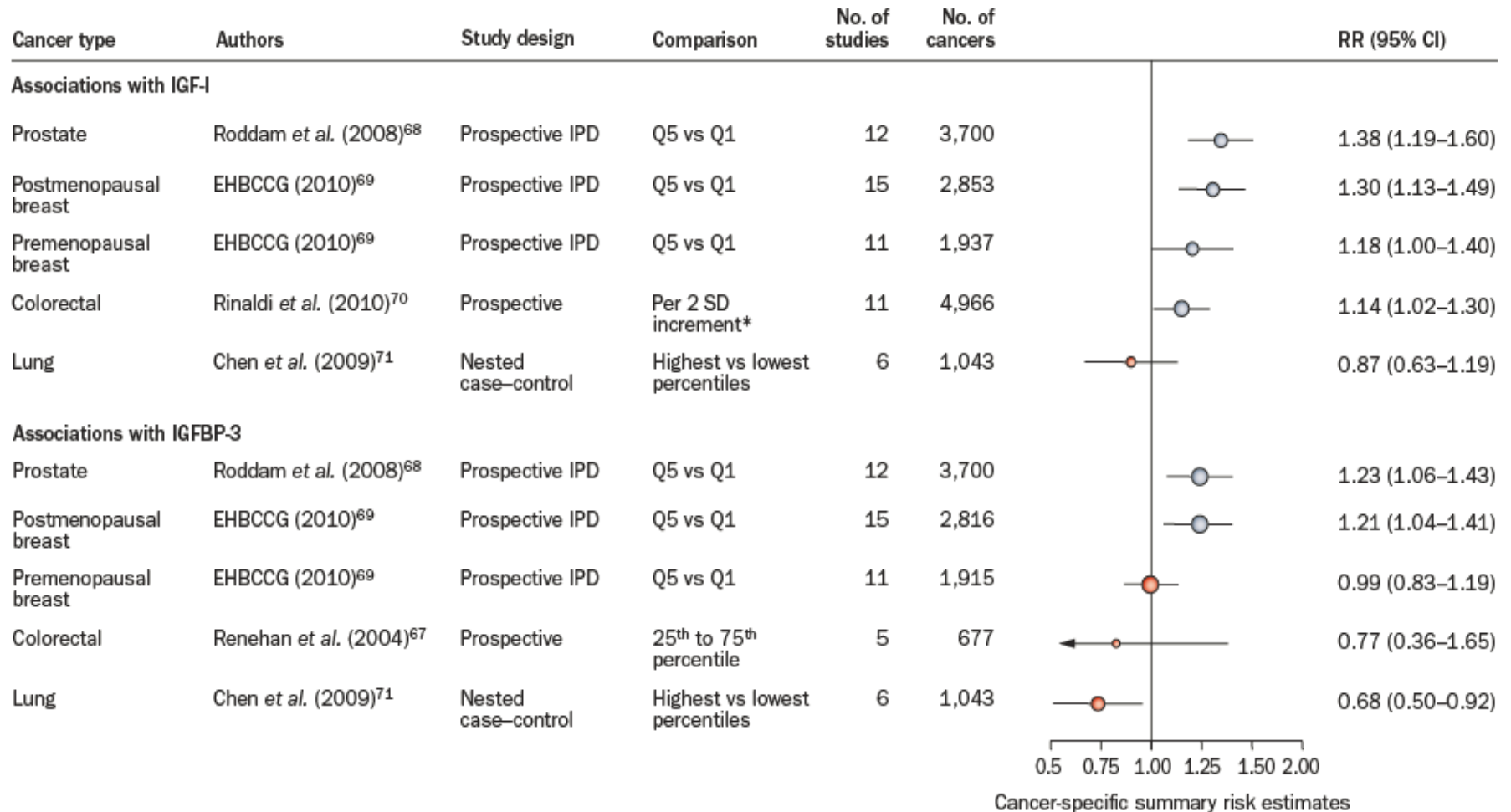
THE LANCET • Vol 363 • April 24, 2004 • www.thelancet.com

Interpretation

Mixed cohort and case-control studies: inconsistent associations;
Questioned negative associations of IGFBP-3 with cancer risk.



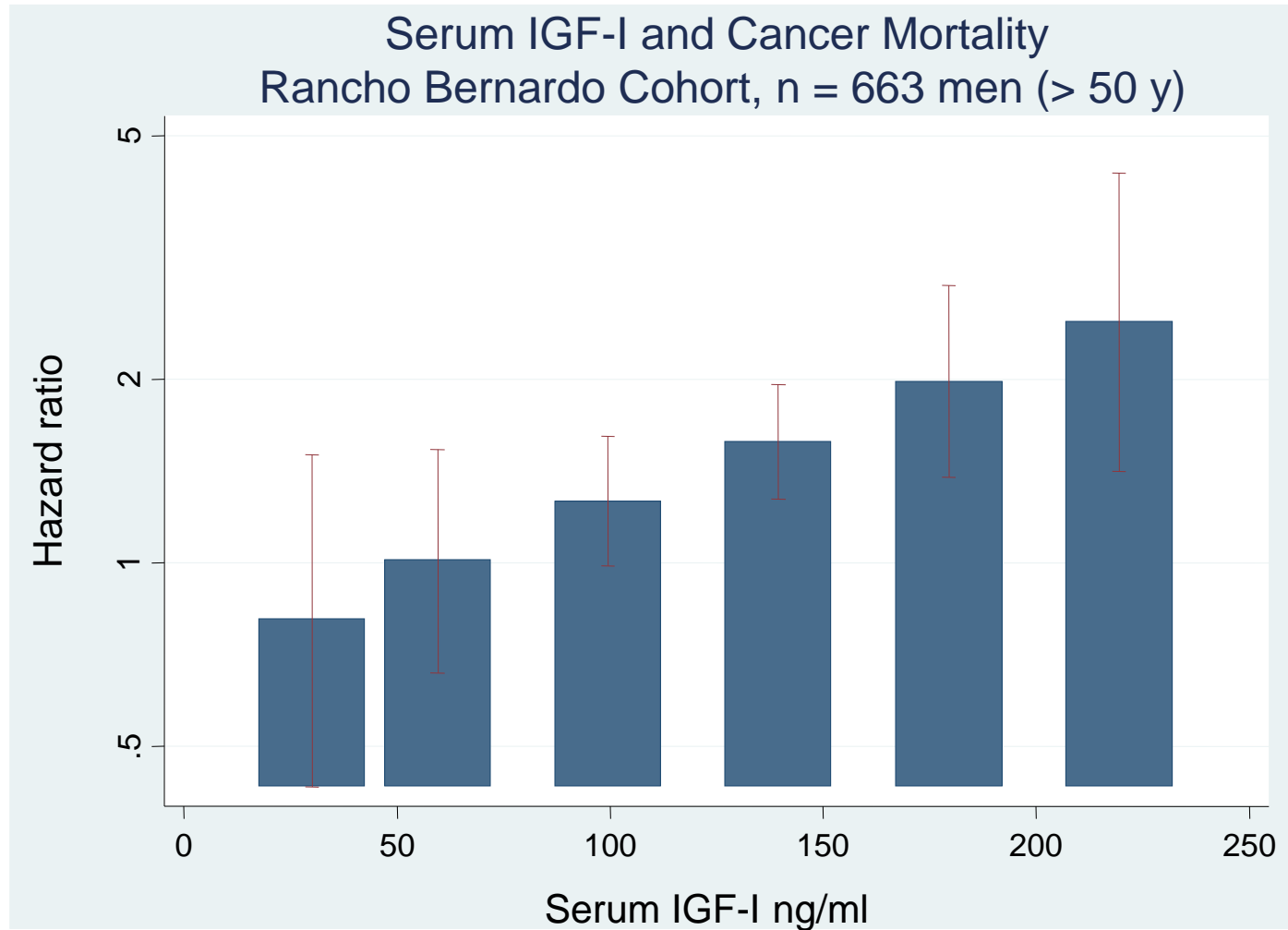
IGF-I, IGFBP-3 & cancer risk update



Clayton, Banarjee, Murray, Rehnan Nature Reviews Endo 2011;7:11-24



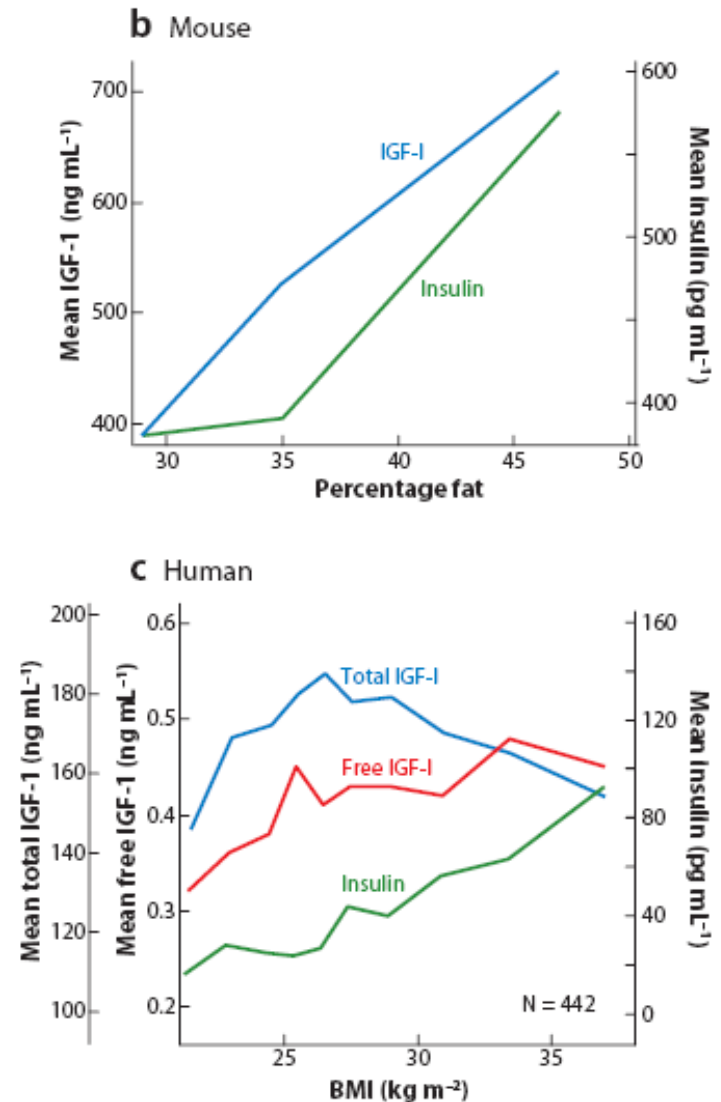
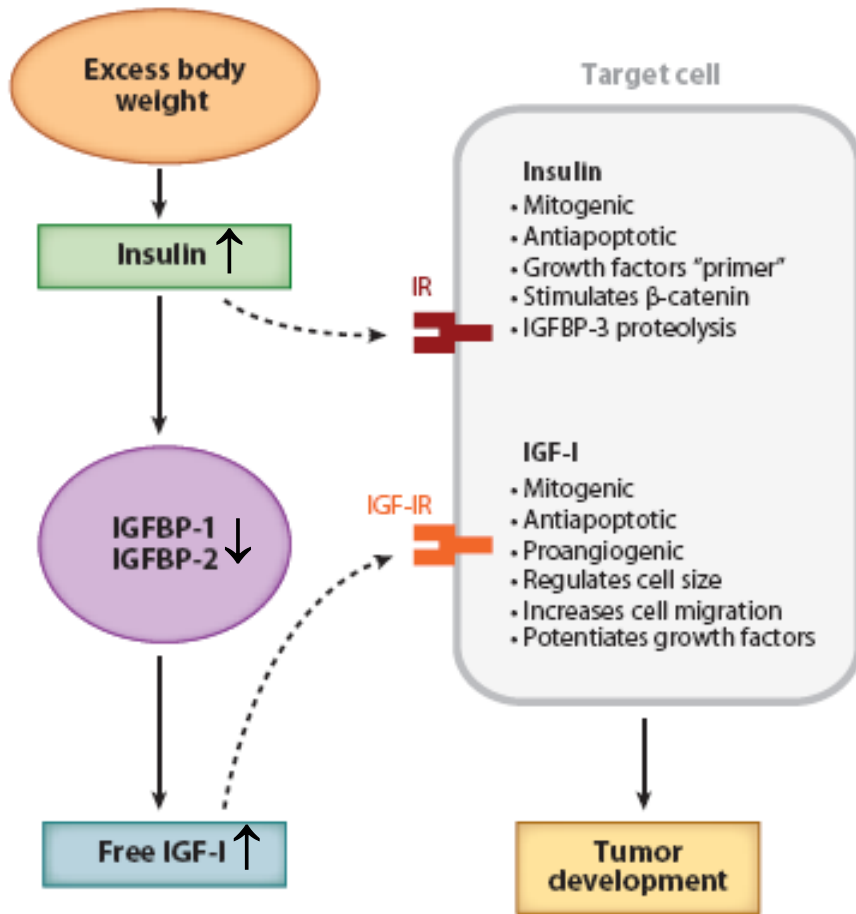
Serum IGF-I & cancer mortality



Major et al. JCEM 2010; 95:1054-59



Insulin-IGF hypothesis



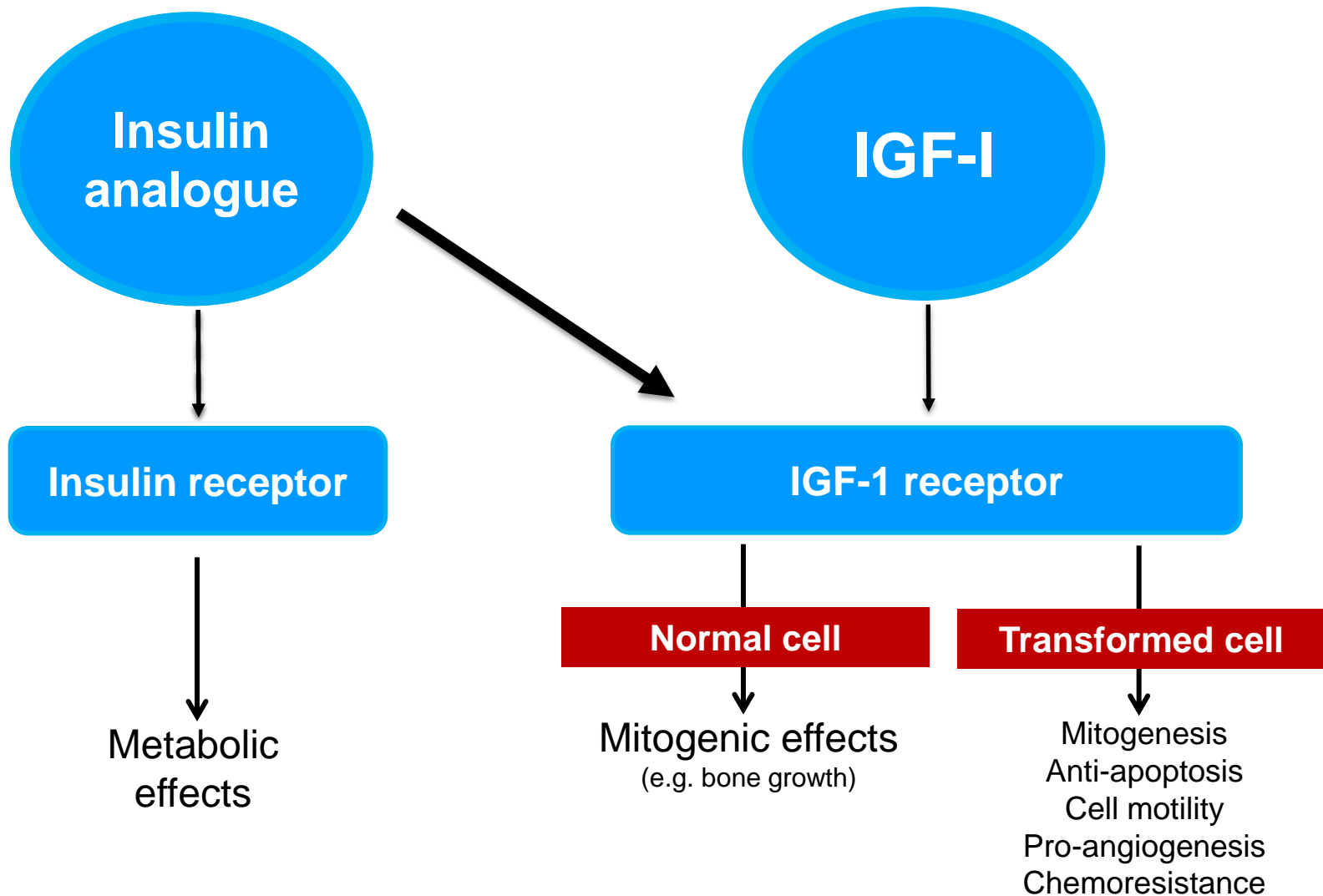


IGF-I & cancer cell biology



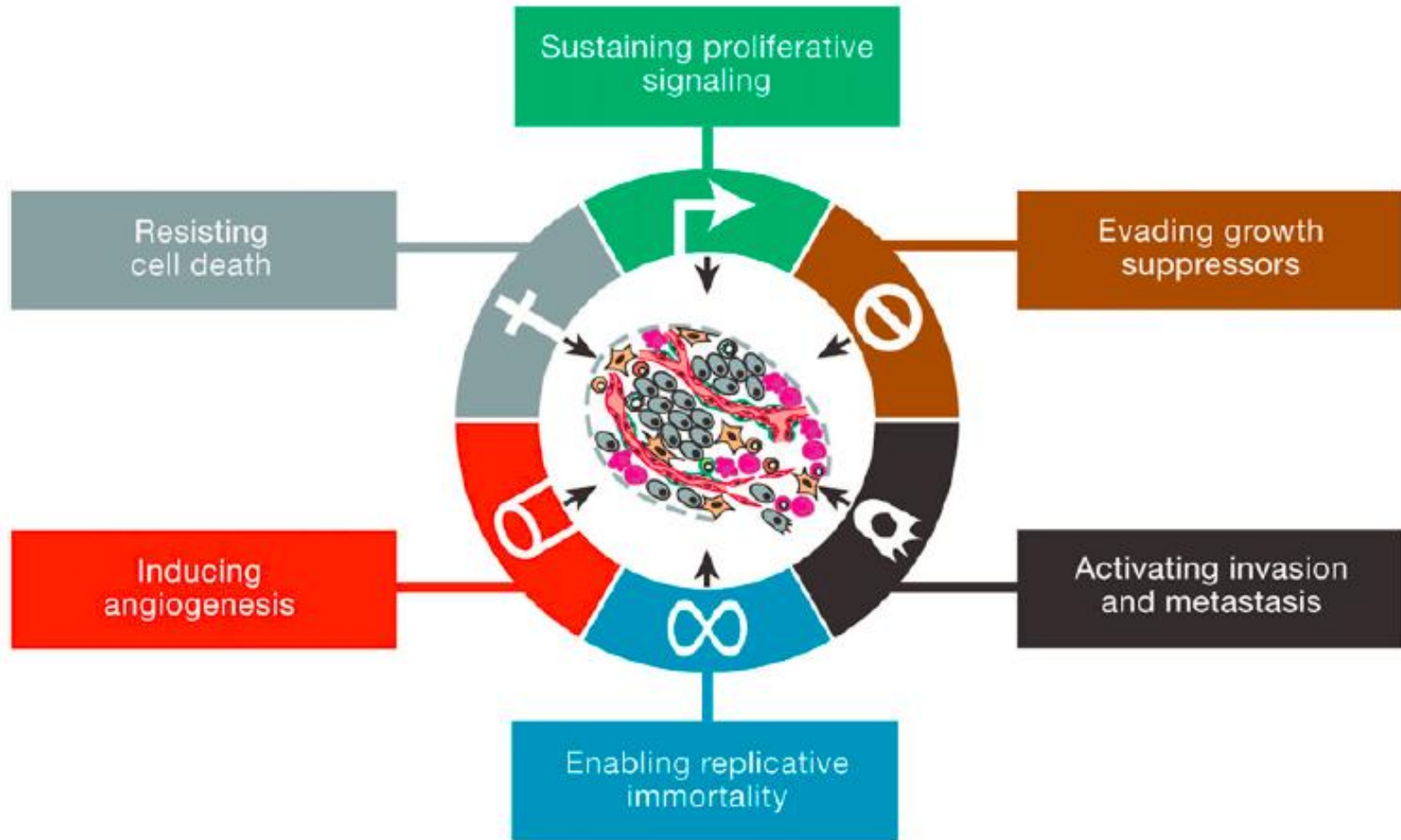


Insulin-IGF-I activation



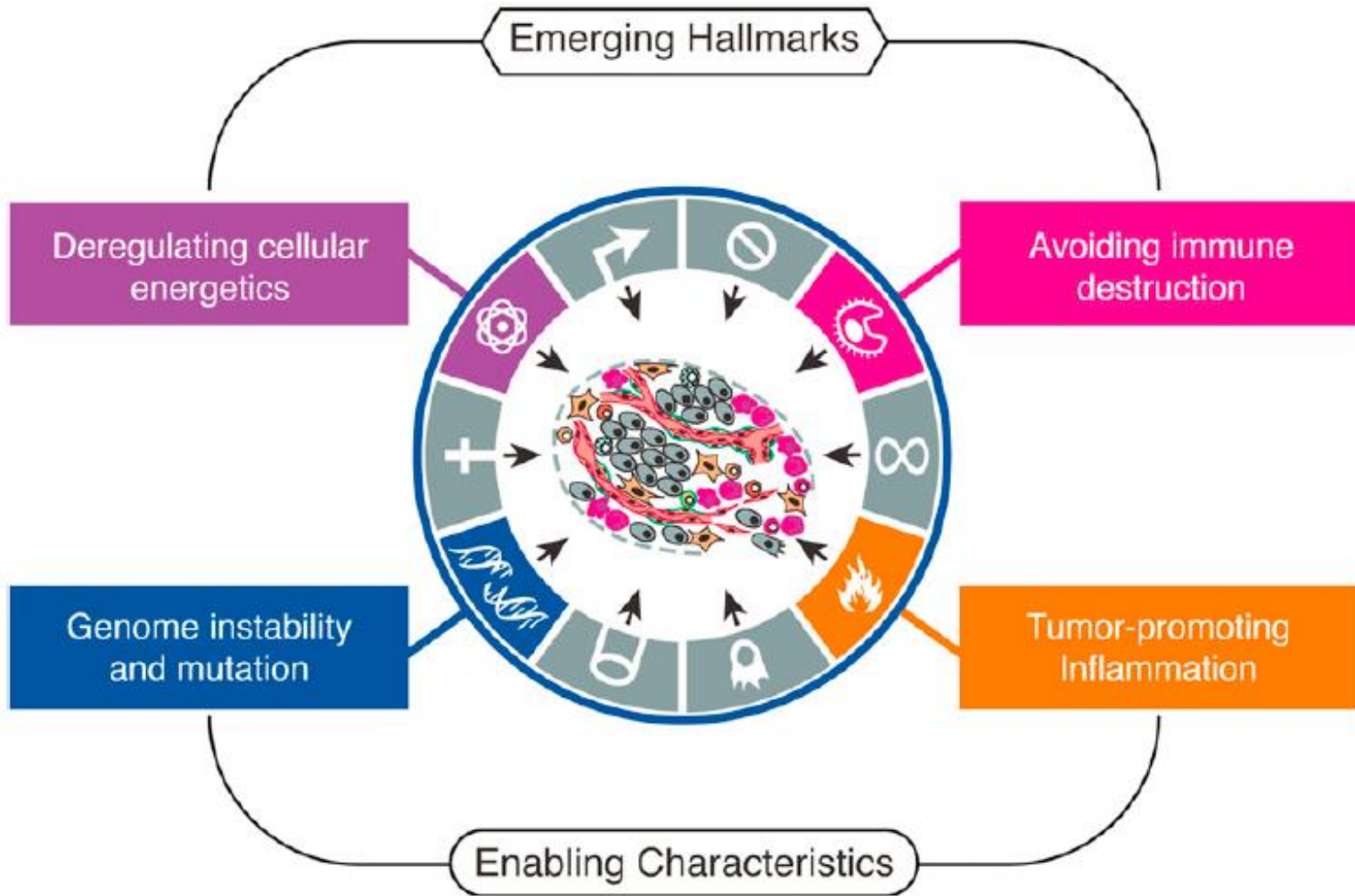


Hallmarks of cancer



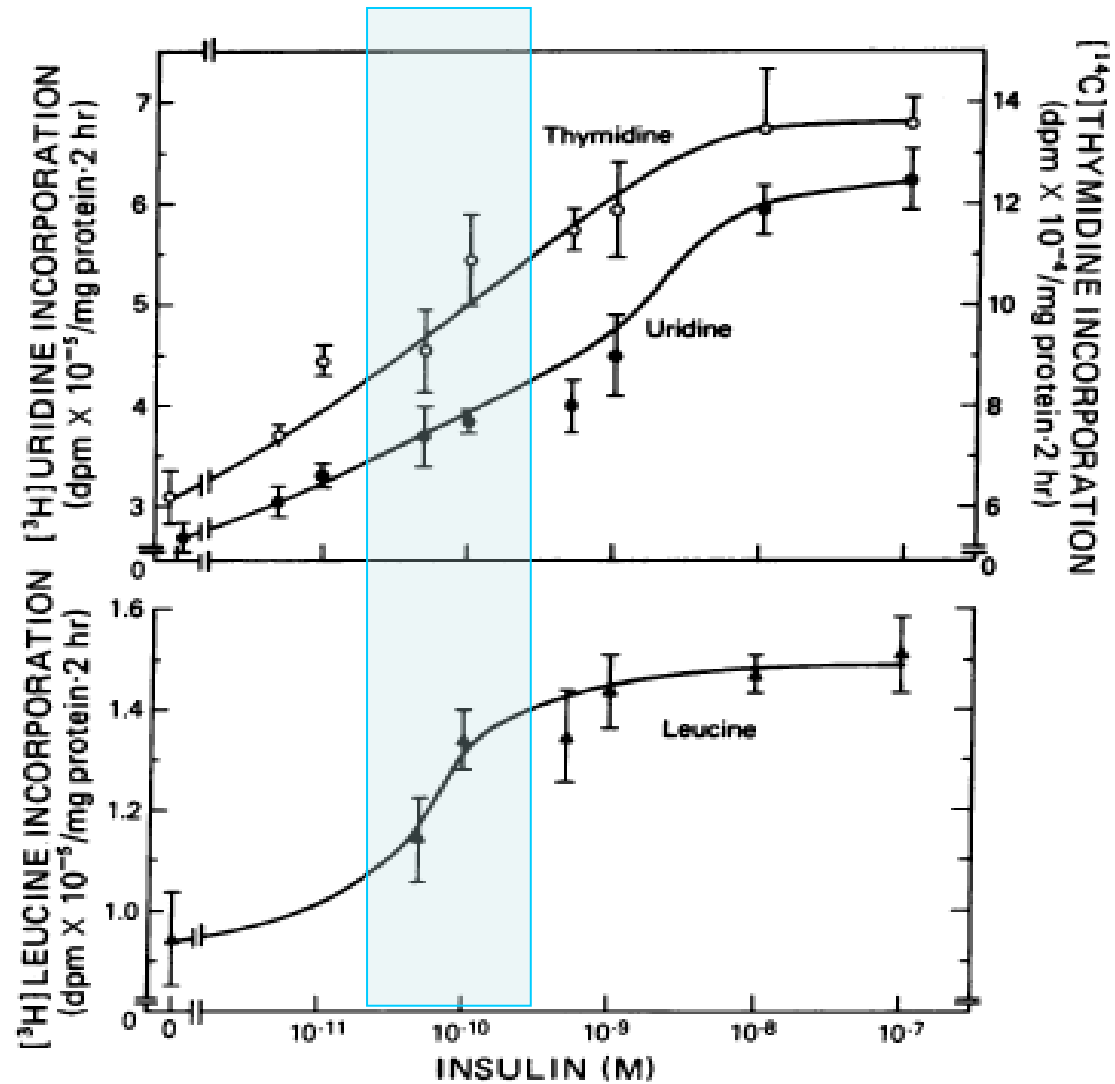


Hallmarks of cancer - update





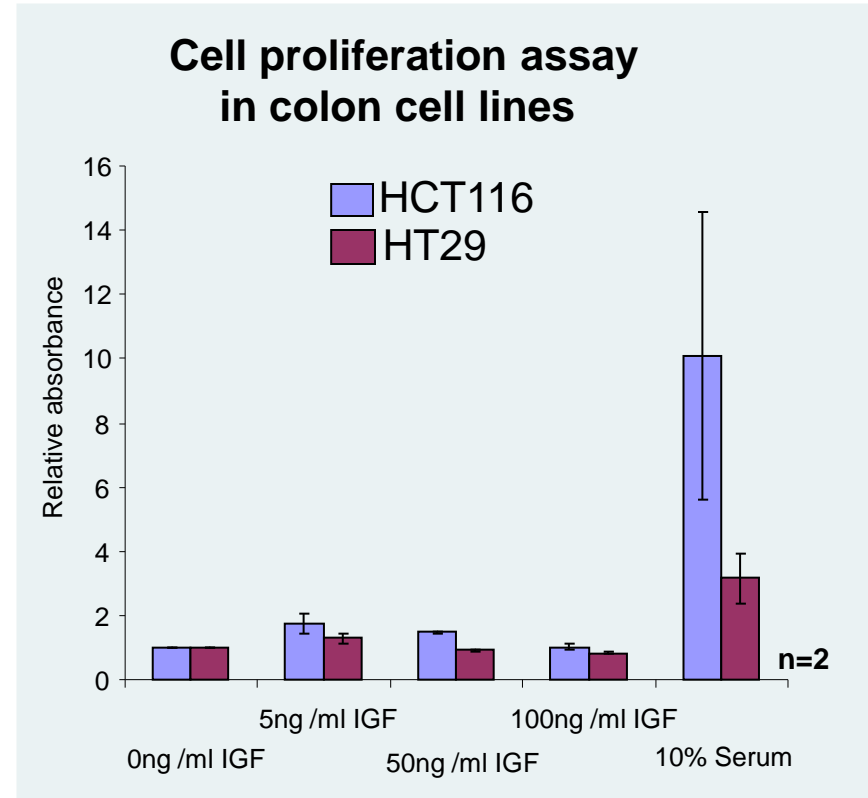
Insulin stimulates breast cancer cells





IGF-I & cell proliferation

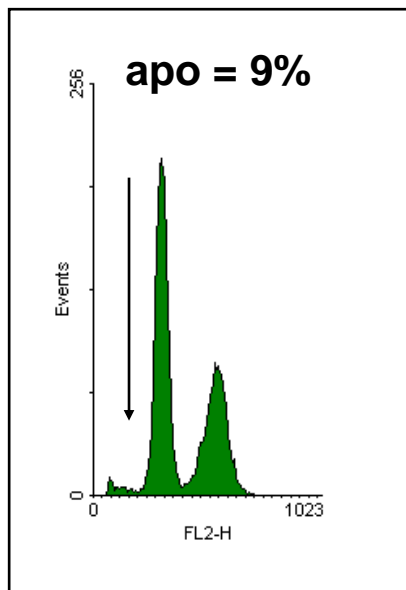
- Definition of mitogenicity
- H³ thymidine = poor concordance
- cell growth v ↑ cell size
- perception that receptor ligand binding ≈ mitogenicity
- variation among cell types



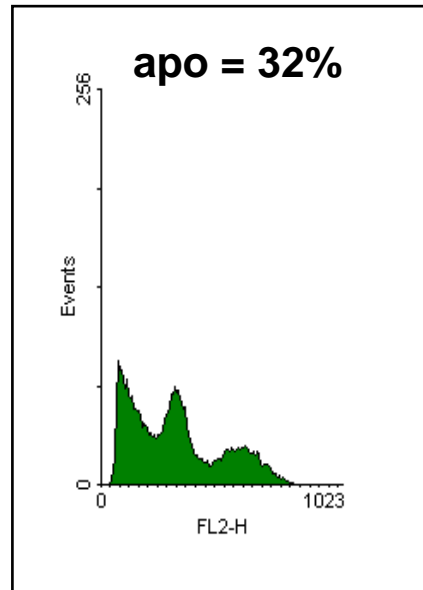


IGF-I & anti- apoptosis

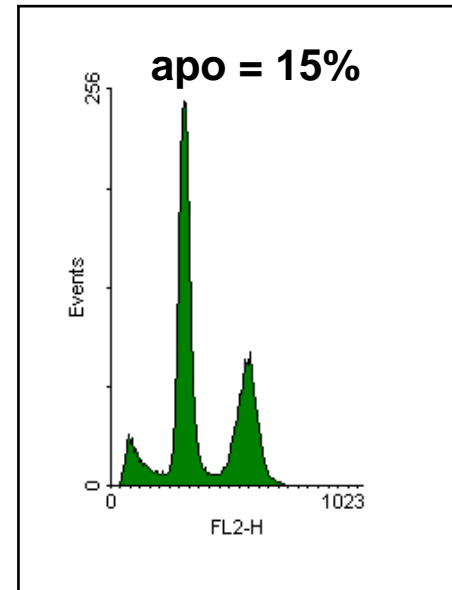
HCT116 cells: γ -irradiation-induced apoptosis (24 h)



Control (SFM)



**RT alone
(10 Gy)**



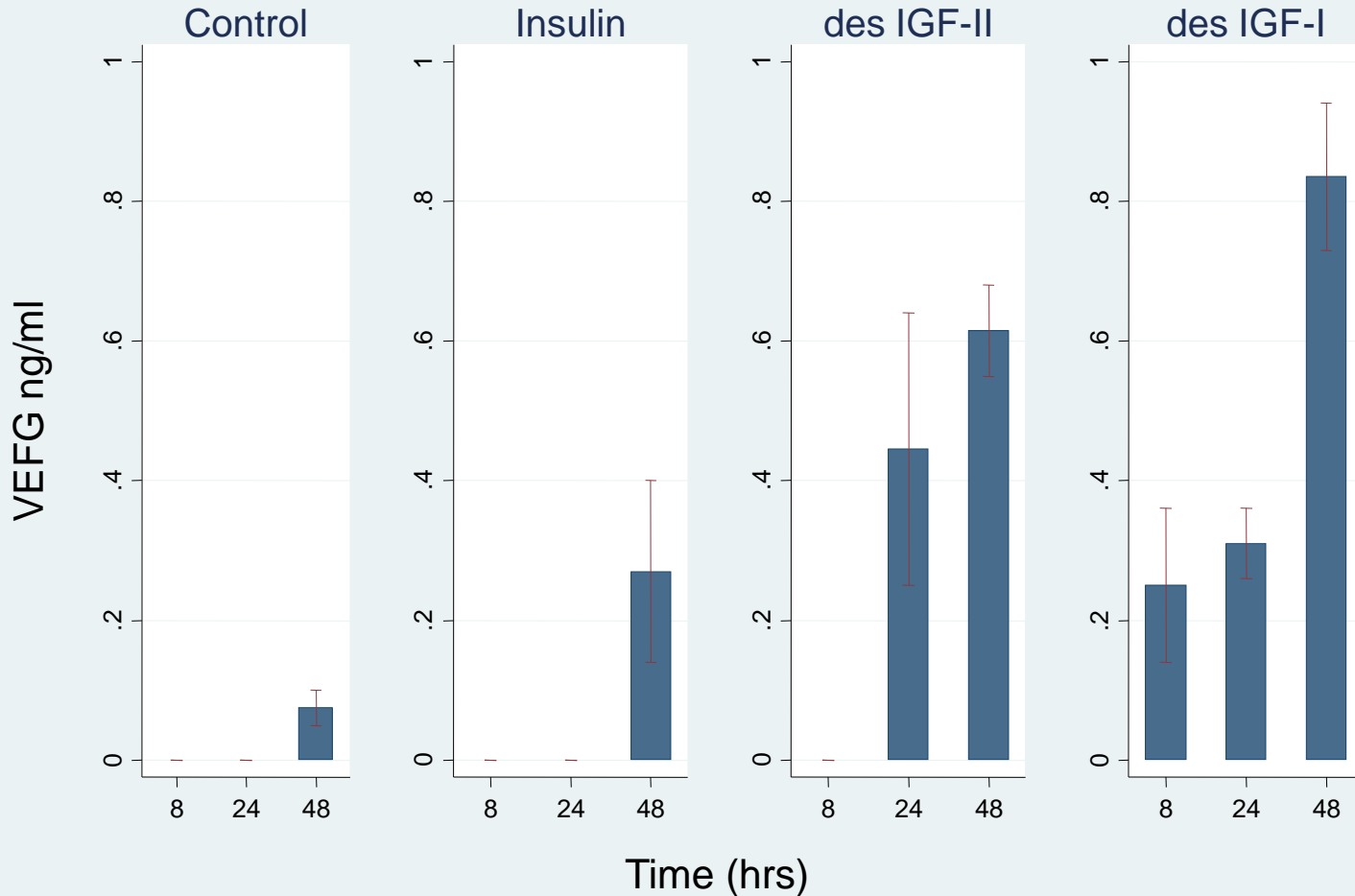
RT + IGF-I (1 nM)



IGF-I & VEGF production

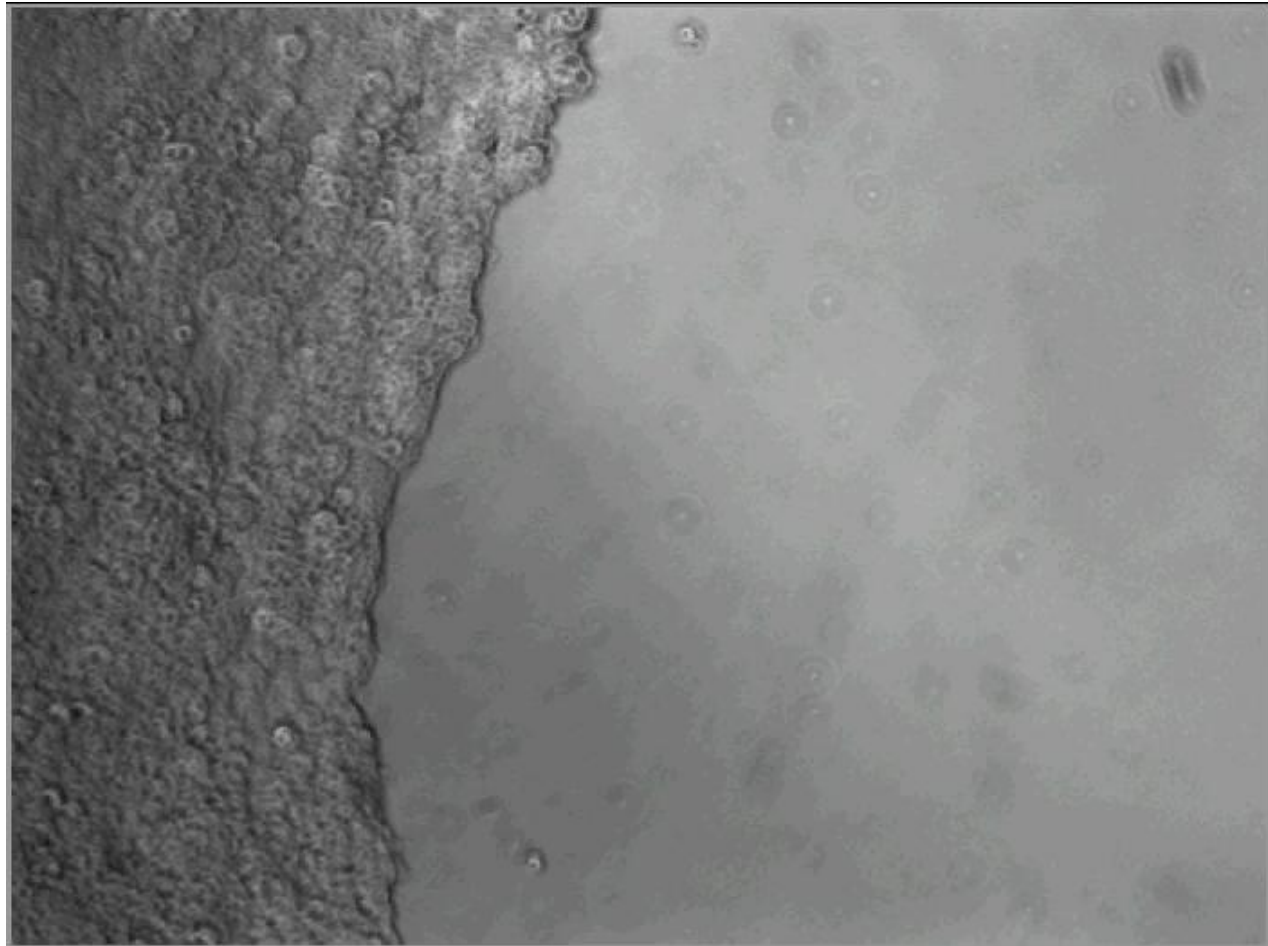
(as a surrogate of angiogenesis potential)

VEGF expression in cell lysates, HCT116 colon cancer cells





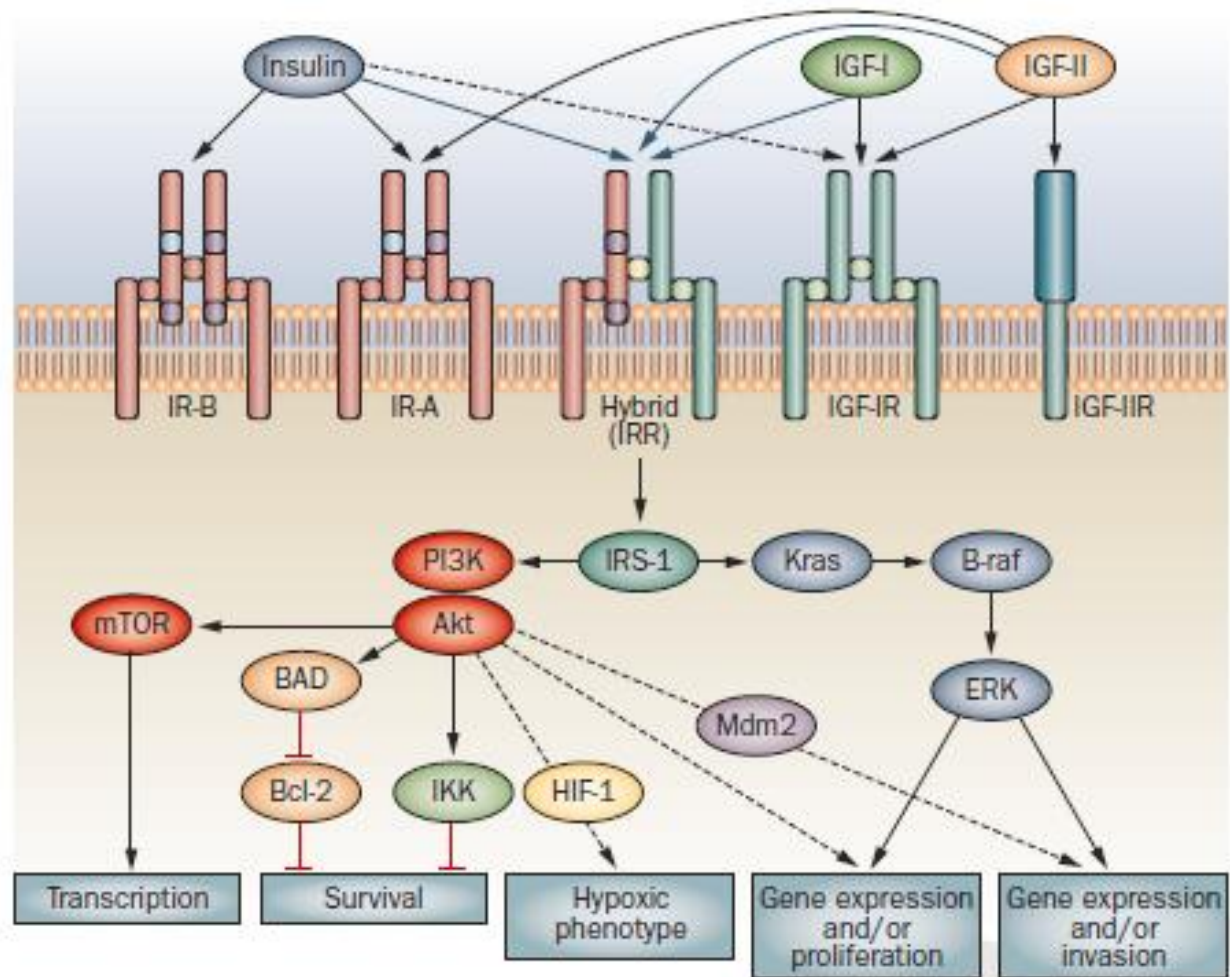
IGF-I & cell migration



HCT116 – 50ng/ml IGF-1 over 24 hours in confluent culture



IGF-I actions

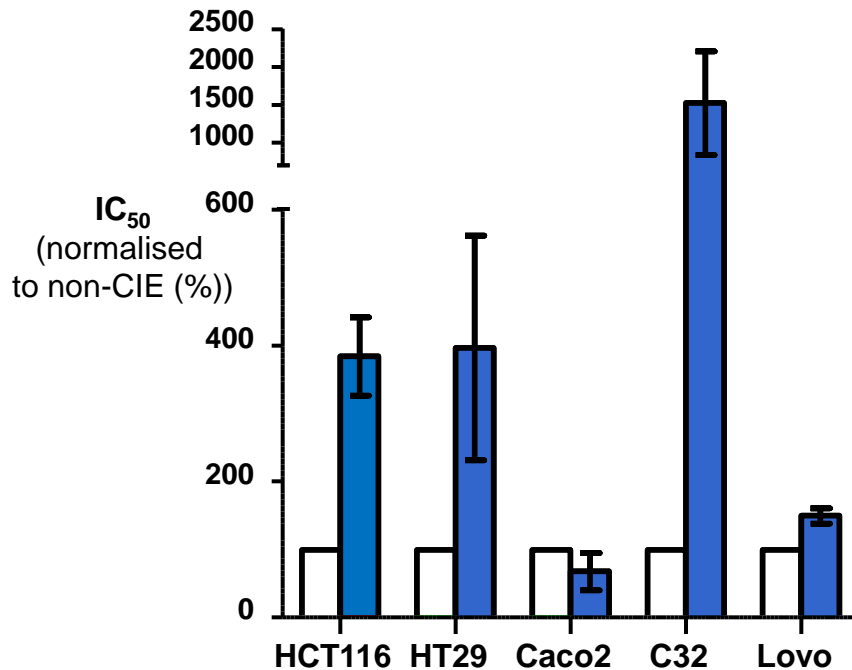


Cleyton, Banarjee, Murray, Renehan Nature Reviews Endo in press

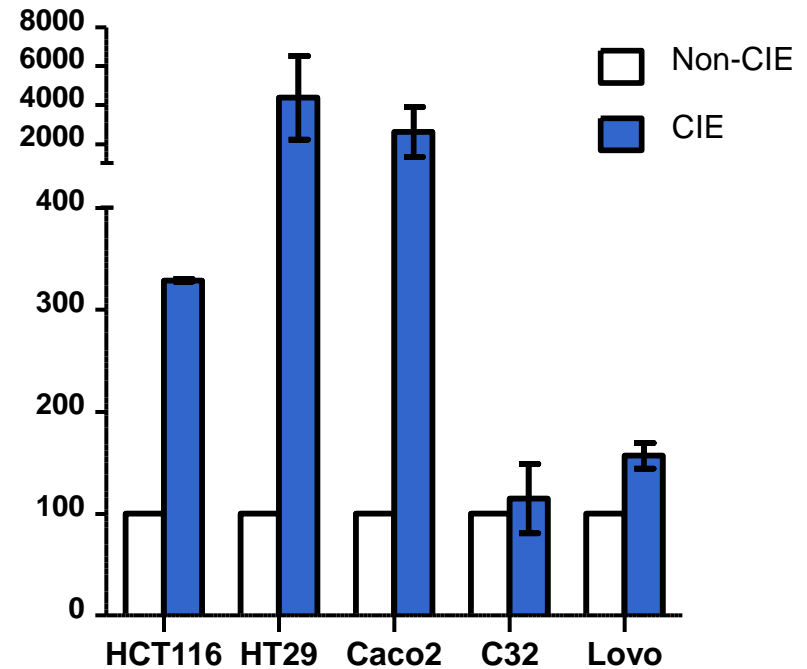


Insulin and chemo-resistance

Oxaliplatin



SN38 (Irinotecan)





Summary

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Clinical implications





What can we tell our patients

Develop local diabetes-oncology protocol

What may be in these protocols?

1. In the diabetic patient w.o. cancer – in general, the message is reassurance regarding insulin analogues
2. Pathways for routine cancer screening in diabetic patients
3. In diabetic patients with cancer – review medications & risk factors (e.g. BMI, smoking) regularly
4. In non-diabetic cancer patients, encourage trial recruitment e.g. to metformin adjuvant trials



Thank you

