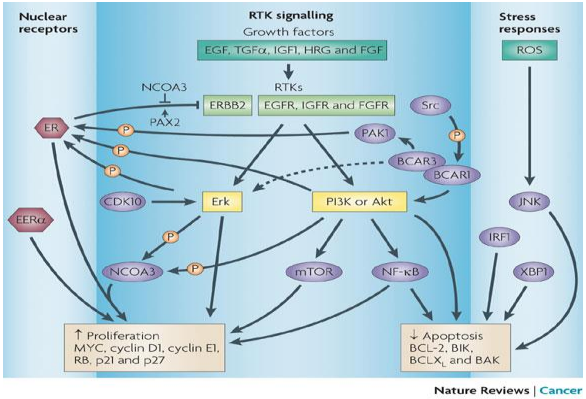
University of BRISTOL

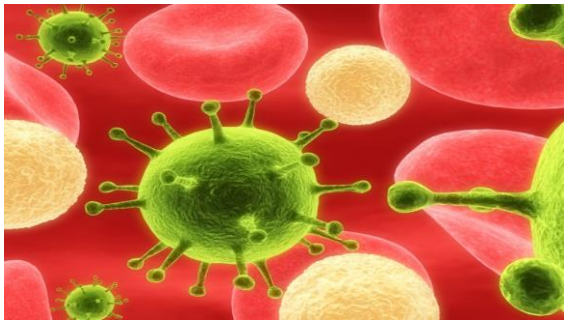
World Cancer Research Fund International

Linking diet, nutrition and physical activity to cancer risk: a systematic review framework for integrating evidence from human, animal and other mechanistic studies

Aim

To develop and publish a framework for carrying out rigorous systematic reviews of mechanistic studies.





Why is this important?

- Wealth of data on potential mechanisms often not taken into account.
- Methods for combining information from human, animal and cell studies are lacking.
- Need to identify gaps in the research.

Hypothesis to be explored:

High milk consumption is a risk factor for prostate cancer

Analytical approach

- Large multi-disciplinary group
- 5 workshops -mixture of presentations with discussion, small group exercises, round table discussions
- On going searches, and development of methods, feedback to members of the team
- Regular meetings between PIs and research associates

Stage 1-
Search for mechanisms

Searching for studies

Incorporate an exhaustive list of mechanistic targets (**intermediate phenotypes**-eg hallmarks of cancer, hormones etc)

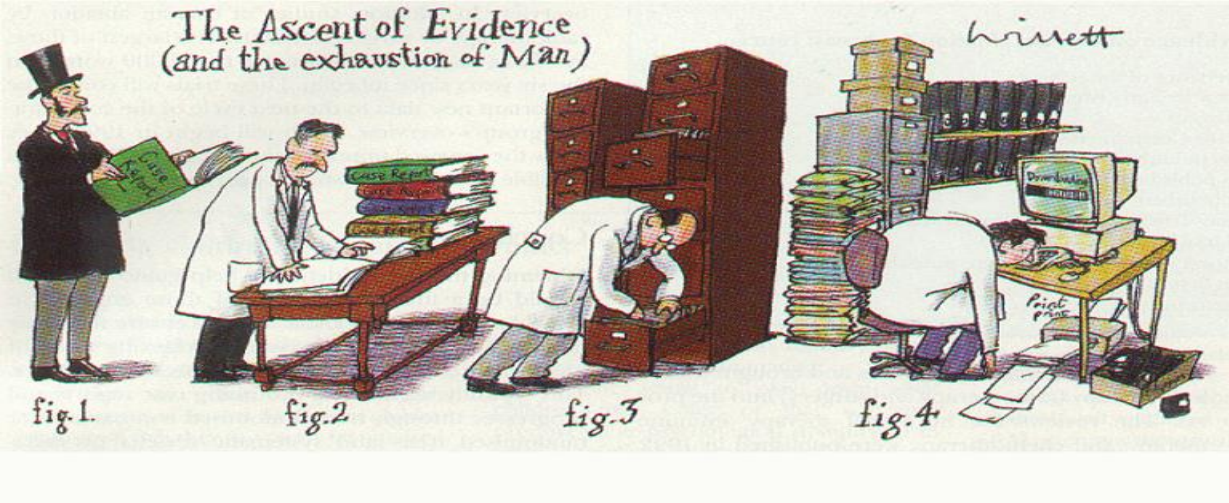
Three sets of searches:

Exposure-Outcome (E → O)

Exposure-Intermediate phenotype (E → IP)

Intermediate phenotype and Outcome (IP →O)

Why automate the search for mechanisms?

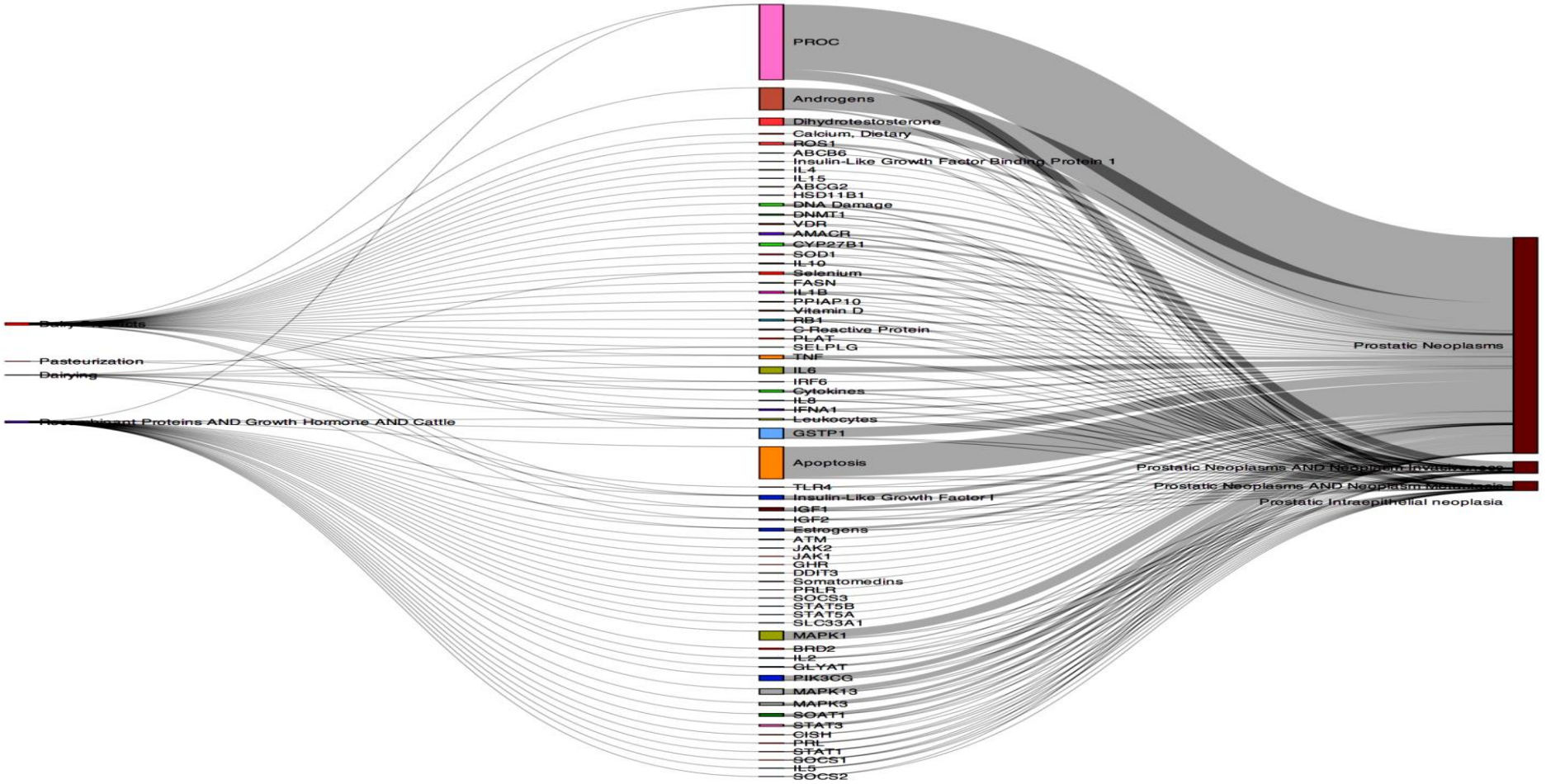


Introducing **TeMMPo: Text Mining for Mechanism Prioritisation -Tom Gaunt**

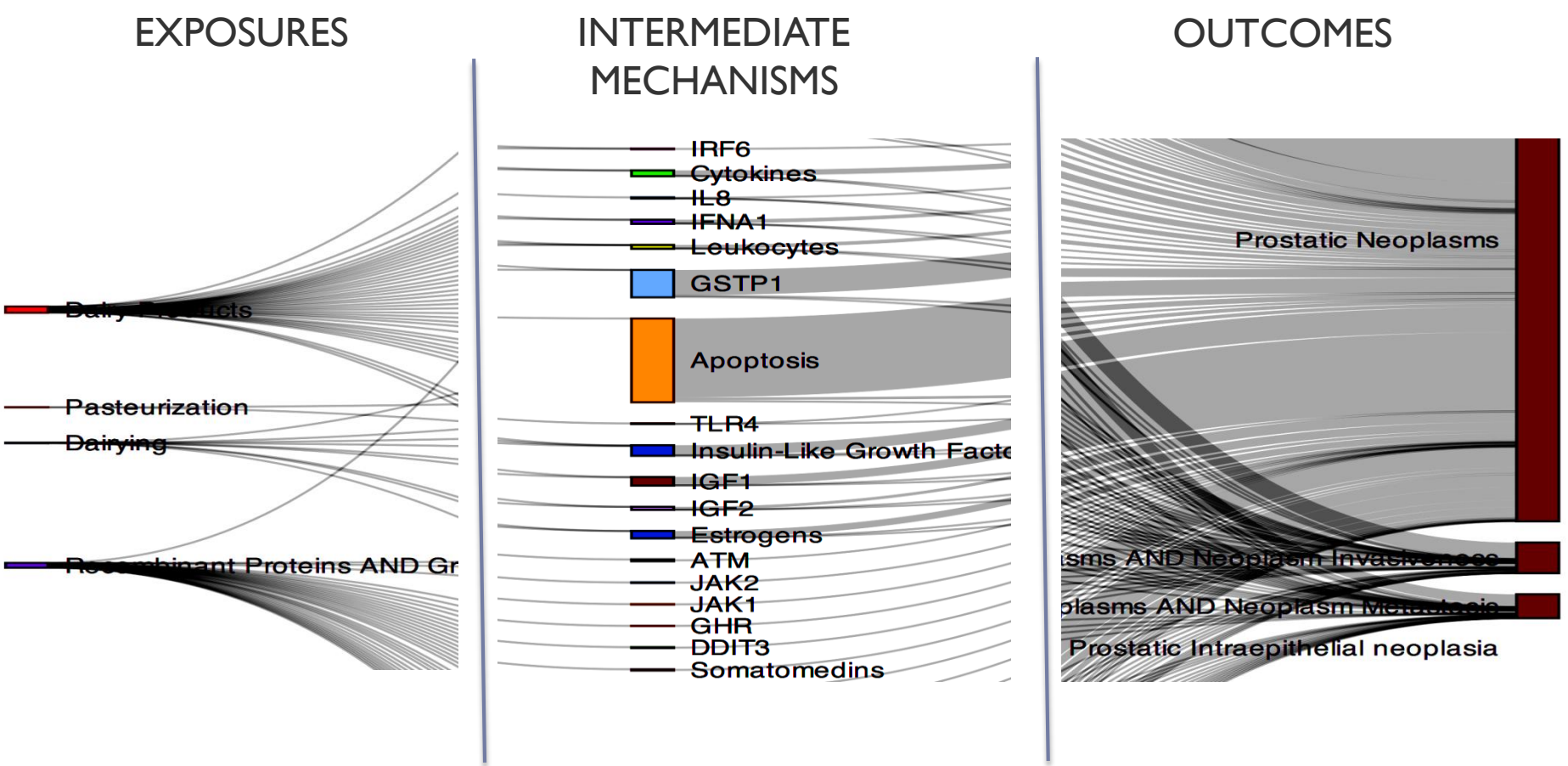
- Identifies co-occurrence of MESH headings in scientific publications to indicate papers that link an intermediate mechanism to either an exposure or an outcome.

- https://www.temmpo.org.uk/

Sankey plot


Pasteurization
Dairying
Recombinant Proteins AND Growth Hormone AND Cattle
PROC
Androgens
Dihydrotestosterone
Calcium, Dietary
ROS1
ABCB6
Insulin-Like Growth Factor Binding Protein 1
IL4
IL15
ABCG2
HSD11B1
DNA Damage
DNMT1
VDR
AMACR
CYP27B1
SOD1
IL10
Selenium
FASN
IL1B
PPIAP10
Vitamin D
RB1
C-Reactive Protein
PLAT
SELPLG
TNF
IL6
IRF6
Cytokines
IL8
IFNA1
Leukocytes
GSTP1
Apoptosis
TLR4
Insulin-Like Growth Factor I
IGF1
IGF2
Estrogens
ATM
JAK2
JAK1
GHR
DDIT3
Somatomedins
PRLR
SOCS3
STAT5B
STAT5A
SLC33A1
MAPK1
BRD2
IL2
GLYAT
PIK3CG
MAPK13
MAPK3
SOAT1
STAT3
GSH
PRL
STAT1
SOCS1
IL5
SOCS2
Prostatic Neoplasms
Prostatic Neoplasms AND Neoplasm Invasiveness
Prostatic Neoplasms AND Neoplasm Metastasis
Prostatic Intraepithelial neoplasia

Automated mechanism quantification and display



Stage 2-Systematic review of a specific mechanism

Step 1: Specify research objectives

Step 2: Search for studies

Step 3: Apply inclusion/exclusion criteria, including an assessment of relevance

Step 4: Extract data

Step 5: Assess the quality of individual studies

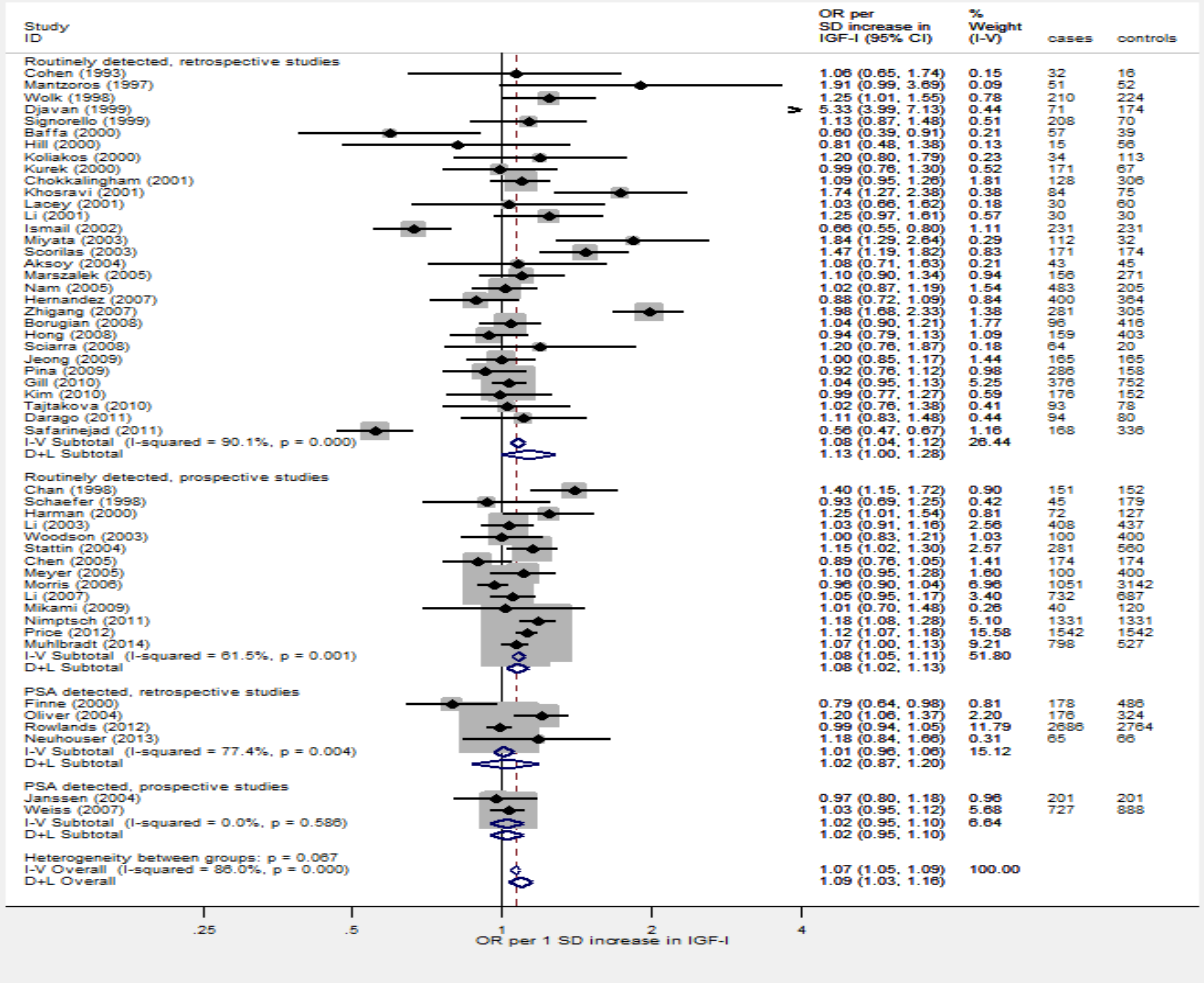
Step 6: Synthesis of data from individual studies

Step 7: Assess strength of overall body of evidence for human and animal studies separately

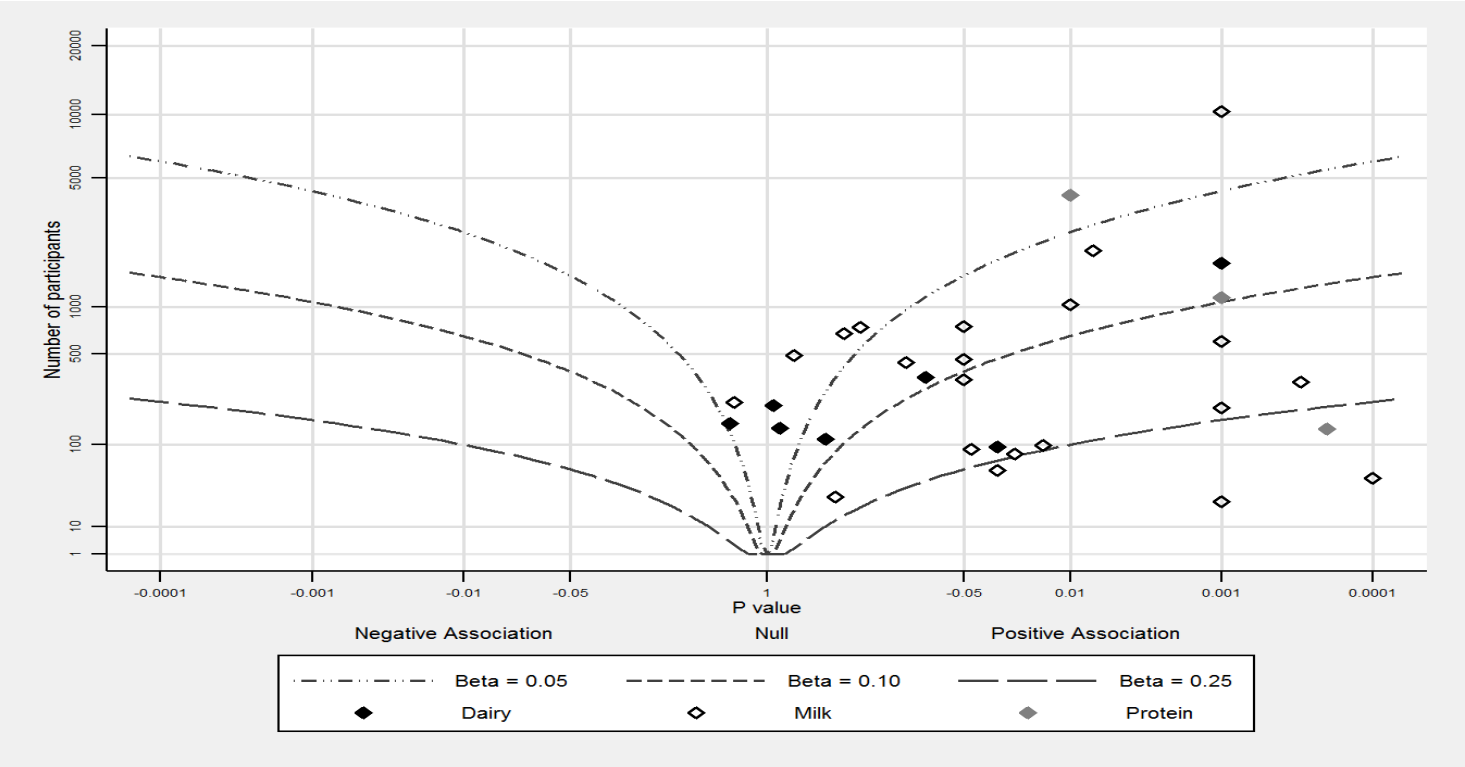
Step 8: Integrate human and animal studies to develop an evidence based conclusion

Step 9: Synthesis of supporting evidence from *in vitro* and xenograft models underpinning biological plausibility

Synthesis of disparate data

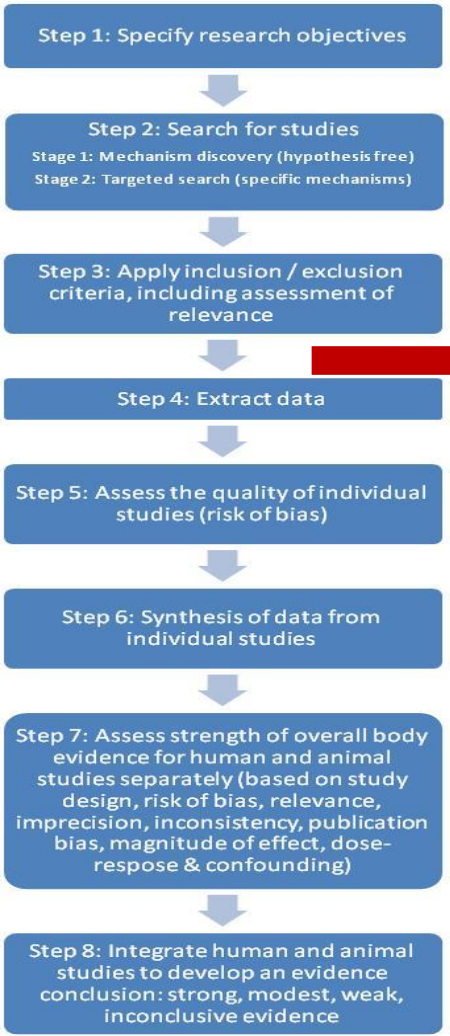

Study ID
OR per SD increase in IGF-I (95% CI)
% Weight (I-V)
cases
controls
Routinely detected, retrospective studies
Cohen (1993) 1.06 (0.65, 1.74) 0.15 32 16
Mantzoros (1997) 1.91 (0.99, 3.69) 0.09 51 52
Wolk (1998) 1.25 (1.01, 1.55) 0.78 210 224
Djavan (1999) 5.33 (3.99, 7.13) 0.44 71 174
Signorello (1999) 1.13 (0.87, 1.48) 0.51 208 70
Baffa (2000) 0.60 (0.39, 0.91) 0.21 57 39
Hill (2000) 0.81 (0.48, 1.38) 0.13 15 56
Koliakos (2000) 1.20 (0.80, 1.79) 0.23 34 113
Kurek (2000) 0.99 (0.76, 1.30) 0.52 171 67
Chokkalingham (2001) 1.09 (0.95, 1.26) 1.81 328 306
Khosravi (2001) 1.74 (1.27, 2.38) 0.38 84 75
Lacey (2001) 1.03 (0.66, 1.62) 0.18 30 60
Li (2001) 1.25 (0.97, 1.61) 0.57 30 30
Ismail (2002) 0.66 (0.55, 0.80) 1.11 231 231
Miyata (2003) 1.84 (1.29, 2.64) 0.29 112 32
Scorilas (2003) 1.47 (1.19, 1.82) 0.83 171 174
Aksoy (2004) 1.08 (0.71, 1.63) 0.21 43 45
Marszalek (2005) 1.10 (0.90, 1.34) 0.94 156 271
Nam (2005) 1.02 (0.87, 1.19) 1.54 483 205
Hernandez (2007) 0.88 (0.72, 1.09) 0.84 400 364
Zhigang (2007) 1.98 (1.68, 2.33) 1.38 281 305
Borugian (2008) 1.04 (0.90, 1.21) 1.77 96 416
Hong (2008) 0.94 (0.79, 1.13) 1.09 159 403
Sciarra (2008) 1.20 (0.76, 1.87) 0.18 64 20
Jeong (2009) 1.00 (0.85, 1.17) 1.44 165 165
Pina (2009) 0.92 (0.76, 1.12) 0.98 286 158
Gill (2010) 1.04 (0.95, 1.13) 5.25 376 752
Kim (2010) 0.99 (0.77, 1.27) 0.59 176 152
Tajtakova (2010) 1.02 (0.76, 1.38) 0.41 93 78
Darago (2011) 1.11 (0.83, 1.48) 0.44 94 80
Safarinejad (2011) 0.56 (0.47, 0.67) 1.16 168 336
I-V Subtotal (I-squared = 90.1%, p = 0.000) 1.08 (1.04, 1.12) 26.44
D+L Subtotal 1.13 (1.00, 1.28)
Routinely detected, prospective studies
Chan (1998) 1.40 (1.15, 1.72) 0.90 151 152
Schaefer (1998) 0.93 (0.69, 1.25) 0.42 45 179
Harman (2000) 1.25 (1.01, 1.54) 0.81 72 127
Li (2003) 1.03 (0.91, 1.16) 2.56 408 437
Woodson (2003) 1.00 (0.83, 1.21) 1.03 100 400
Stattin (2004) 1.15 (1.02, 1.30) 2.57 281 560
Chen (2005) 0.89 (0.76, 1.05) 1.41 174 174
Meyer (2005) 1.10 (0.95, 1.28) 1.60 100 400
Morris (2006) 0.96 (0.90, 1.04) 6.96 1051 3142
Li (2007) 1.05 (0.95, 1.17) 3.40 732 687
Mikami (2009) 1.01 (0.70, 1.48) 0.26 40 120
Nimptsch (2011) 1.18 (1.08, 1.28) 5.10 1331 1331
Price (2012) 1.12 (1.07, 1.18) 15.58 1542 1542
Muhlbradt (2014) 1.07 (1.00, 1.13) 9.21 798 527
I-V Subtotal (I-squared = 61.5%, p = 0.001) 1.08 (1.05, 1.11) 51.80
D+L Subtotal 1.08 (1.02, 1.13)
PSA detected, retrospective studies
Finne (2000) 0.79 (0.64, 0.98) 0.81 178 486
Oliver (2004) 1.20 (1.06, 1.37) 2.20 176 324
Rowlands (2012) 0.99 (0.94, 1.05) 11.79 2686 2764
Neuhouser (2013) 1.18 (0.84, 1.66) 0.31 65 66
I-V Subtotal (I-squared = 77.4%, p = 0.004) 1.01 (0.96, 1.06) 15.12
D+L Subtotal 1.02 (0.87, 1.20)
PSA detected, prospective studies
Janssen (2004) 0.97 (0.80, 1.18) 0.96 201 201
Weiss (2007) 1.03 (0.95, 1.12) 5.68 727 888
I-V Subtotal (I-squared = 0.0%, p = 0.586) 1.02 (0.95, 1.10) 6.64
D+L Subtotal 1.02 (0.95, 1.10)
Heterogeneity between groups: p = 0.067
I-V Overall (I-squared = 86.0%, p = 0.000) 1.07 (1.05, 1.09) 100.00
D+L Overall 1.09 (1.03, 1.16)
.25
.5
1
2
4
OR per 1 SD increase in IGF-I

Albatross plot- milk, dairy products and dairy proteins (exposures) and IGF-I (outcome)- Sean Harrison and Julian Higgins



Assessing the relevance of animal and cell studies to human disease

Question 1 - Has the cancer arisen in the animal model rather than being transplanted into the animal?.



Cell line and animal studies where a tumour is transplanted into the animal model

Supportive evidence from *in vitro* and xenograft models underpinning biological plausibility

Step 7- GRADE -Assessment of the relevance of individual animal studies to the research question being addressed (b)

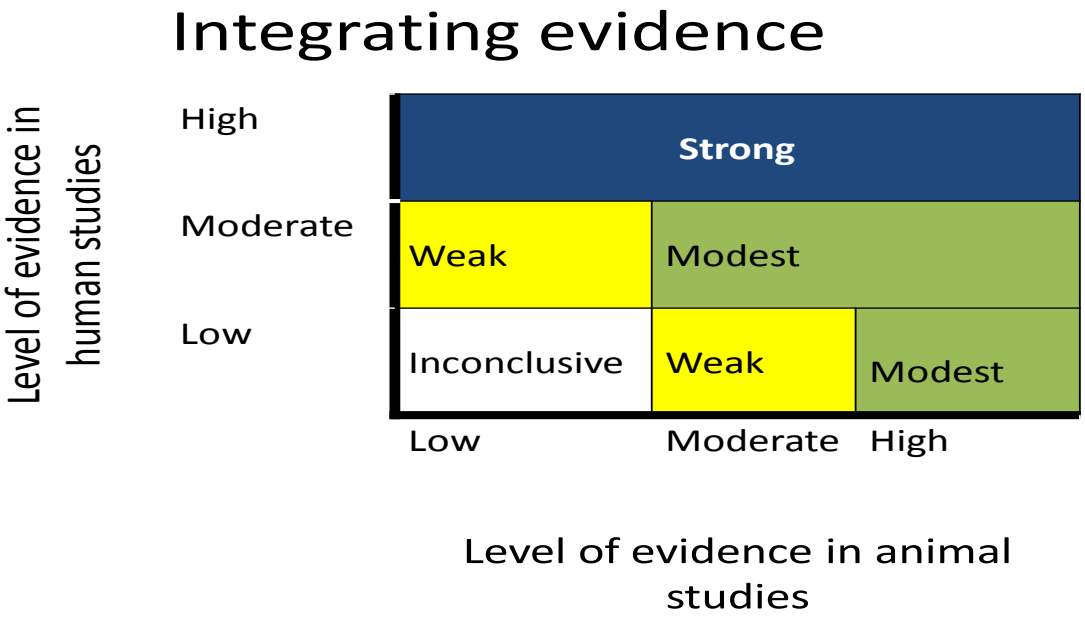
Exposure

- Comparable route?
- Comparable level and frequency?
- Chemically induced tumour model?

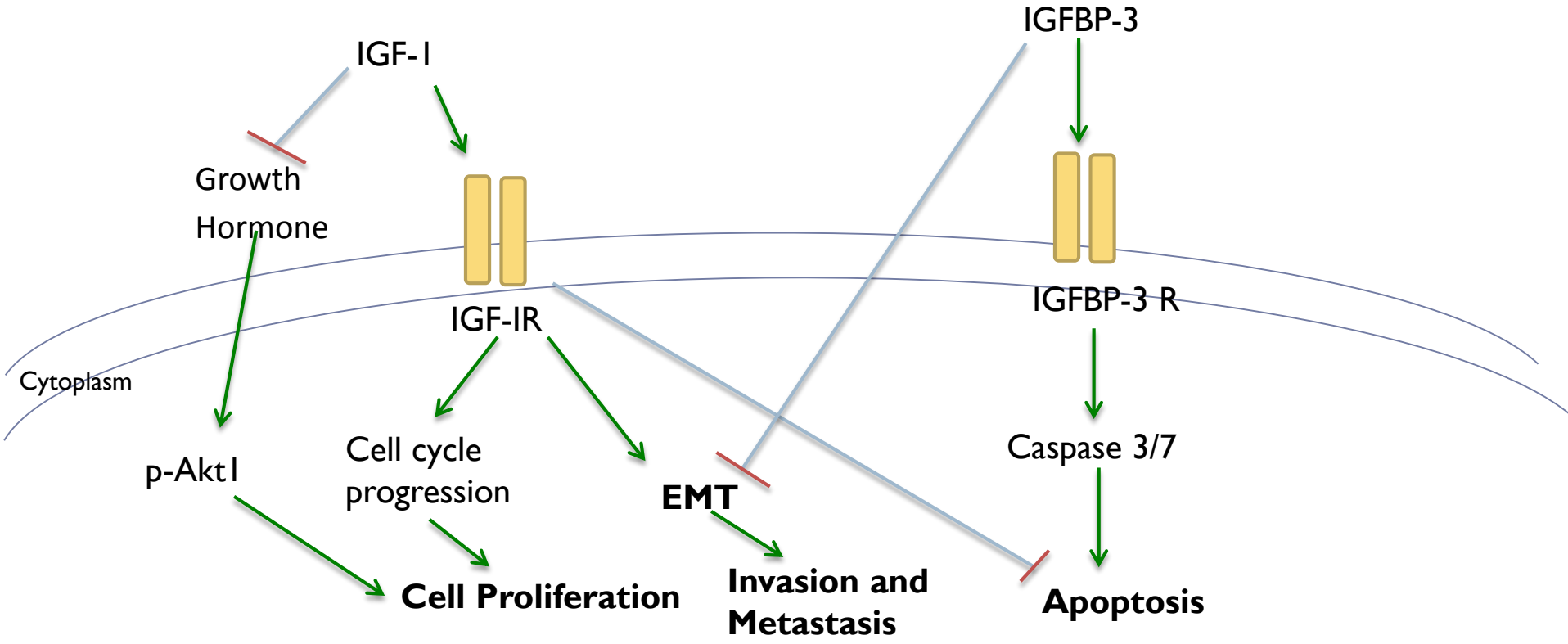
Outcome

- Appropriate follow-up time?
- Does the outcome assessed mimic outcomes in humans?

Stage 2, Step 8- Assessing the strength of evidence across all studies



Potential mechanisms by which IGF system regulates hallmarks of cancer



Future work

- Incorporate changes recommended by validation studies

  Marty Weijenberg -Gökhan Ertaylan and Eline van Roekel

  Rudolf Kaaks- Renée T. Fortner, Audrey Jung, Charlotte Le Cornet

- WCRF funded project -Diet and prostate cancer – mechanistic reviews of BMI and Vit D and PC

- Integrative Cancer Epidemiology – ICEP funded by CRUK – ongoing mechanistic reviews and work on methodology – Julian Higgins

Senior Research Associate Position

Mendelian Randomization and Evidence Synthesis

University of Bristol

3 year post

Immediate start

Closing date- 8th June

Job Ref: ACAD101904

The Team

PI- **Dr Sarah Lewis –**Genetic epidemiology

Co-PI- **Prof Richard Martin** –Epidemiology

Dr Mona Jeffreys- Cancer Epidemiology

Dr Mike Gardner – Animal biology/systematic reviews

Prof Jeff Holly- Molecular biology – IGF and cancer

Dr Claire Perks – Molecular biology

Dr Tom Gaunt – Bioinformatics

Prof Jonathan Sterne- Systematic review methodology

Professor Julian Higgins –Evidence synthesis

Prof Steve Thomas –Head and neck cancer surgeon

Dr Pauline Emmett - Nutritional epidemiology

Dr Kate Northstone – Nutritional Epidemiology

Cath Borwick – Librarian/ Search strategies

Sean Harrison- PhD student

Rosie Lennon-PhD student

Vanessa Tan- PhD student

University of Cambridge
Dr Suzanne Turner-
Animal models

WCRF
Prof Martin Wiseman
Dr Pangiota Mitrou
Dr Rachel Thompson

IARC
Dr Sabina Rinaldi-
Hormones and cancer

Summary of evidence for IGF-I

- There was moderate evidence that circulating IGF-I increases with milk (and dairy protein) intake
- We found a positive association between IGF-I and prostate cancer risk
- IGF-I is a potential mechanism underlying the observed associations between milk intake and prostate cancer risk.

SYRCLE (Systematic Review Centre for Laboratory animal Experimentation) tool

Risk of Bias

- Bias due to confounding
- Bias due to departures from intended intervention (e.g. due to lack of random housing of animals)
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of reported results

Assessing the quality of cell studies

- Validation – authentication of cell lines
- Replication- repeat experiments
- Comparison- experiments carried-out in >1 cell line
- Free from selective reporting