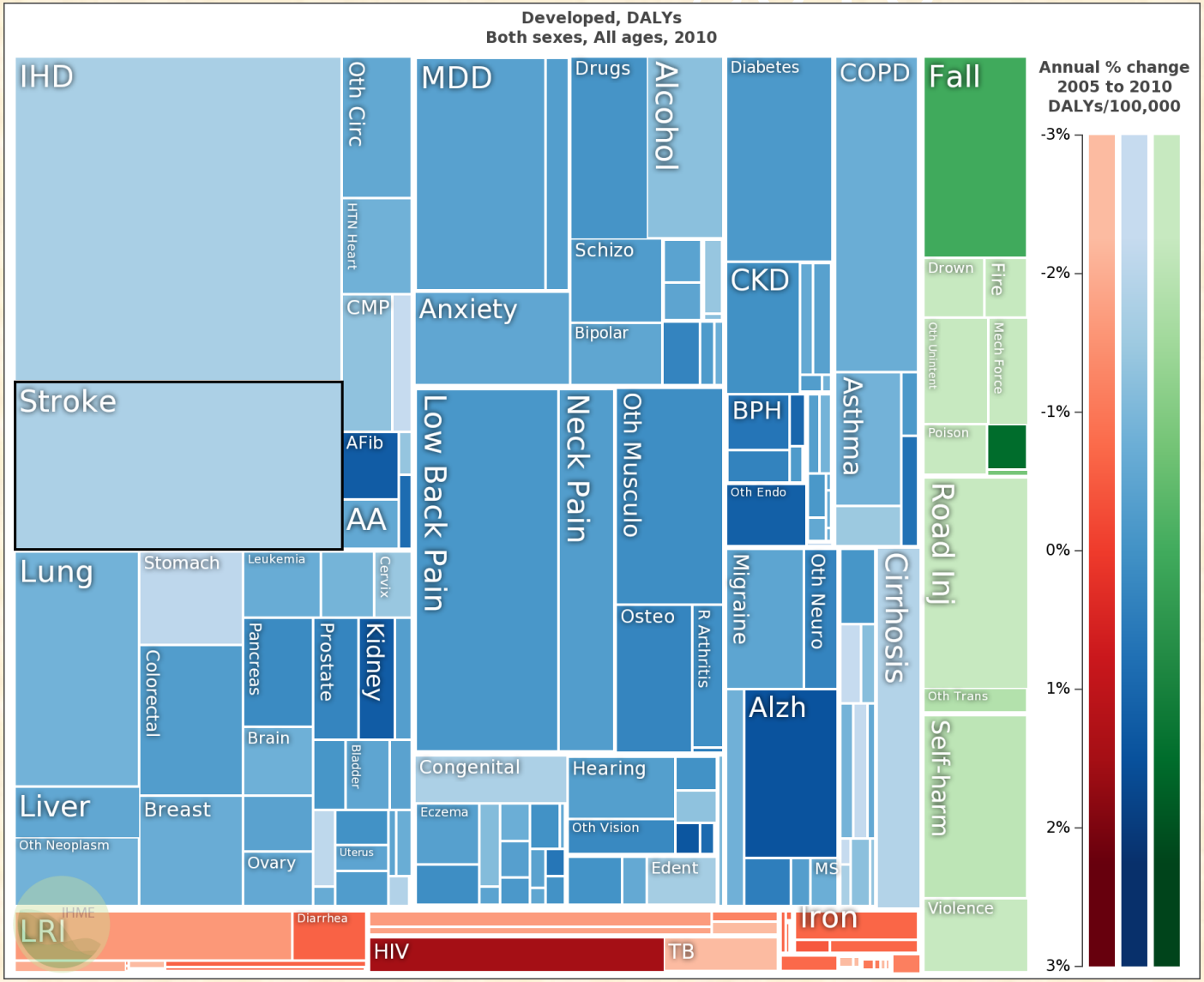
Strategies to get Aging Interventions into Humans

Brian Kennedy
Buck Institute for Research on Aging

DALYs – Developed World 2010



Communicable

Non-communicable

Injuries

http://www.healthmetricsandevaluation.org/tools/data-

What's happening on the Ground?

- Increased Assisted living / Senior Centers
- Aging in Place
- Increased hospitals / healthcare professionals
- Efforts to re-train elders
- Medical monitoring devices
- Emphasis on Rehabilitation Centers
- ……

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What About Keeping People Healthy Longer?

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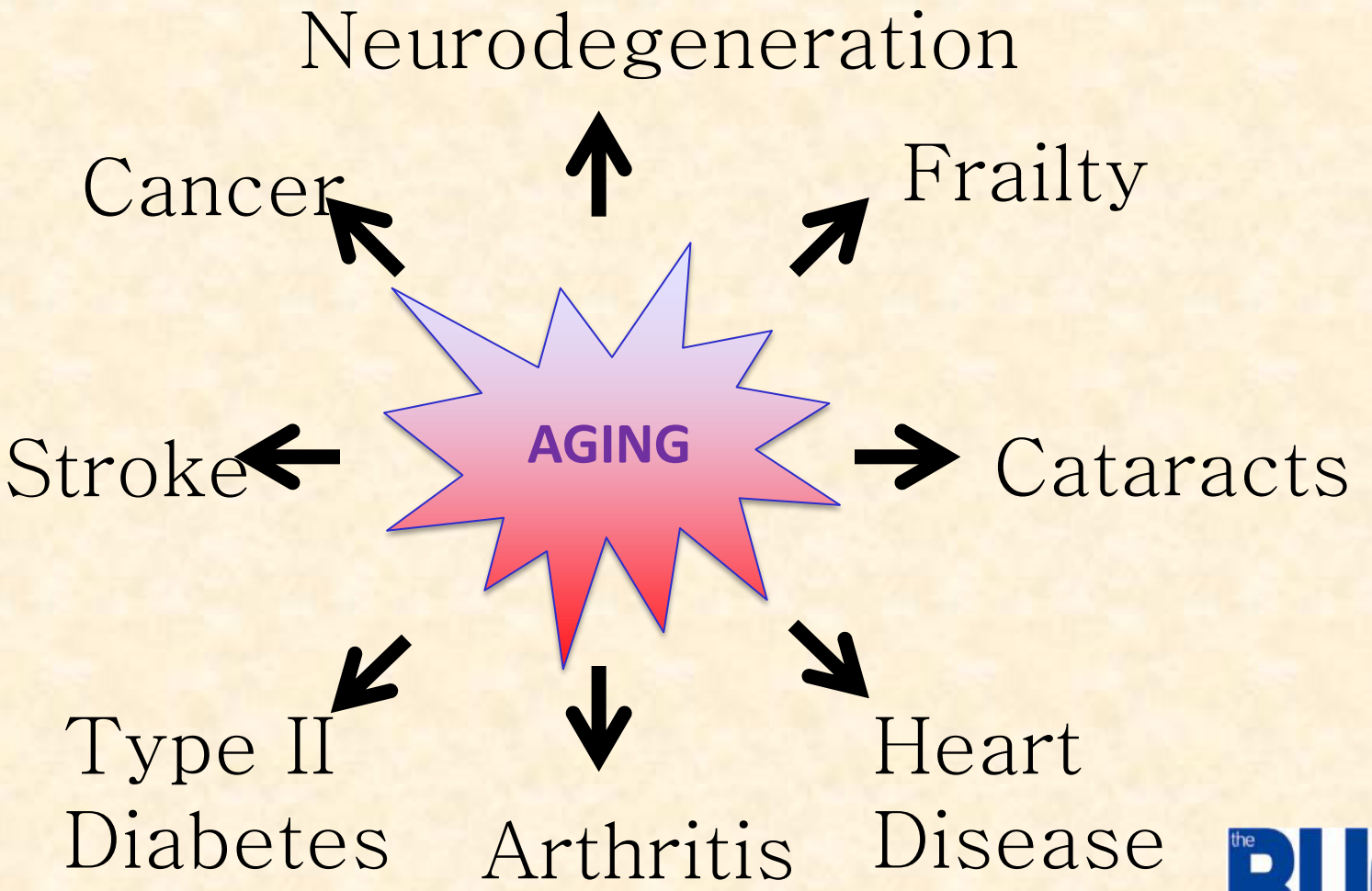
Aging is a driving force in CHRONIC disease



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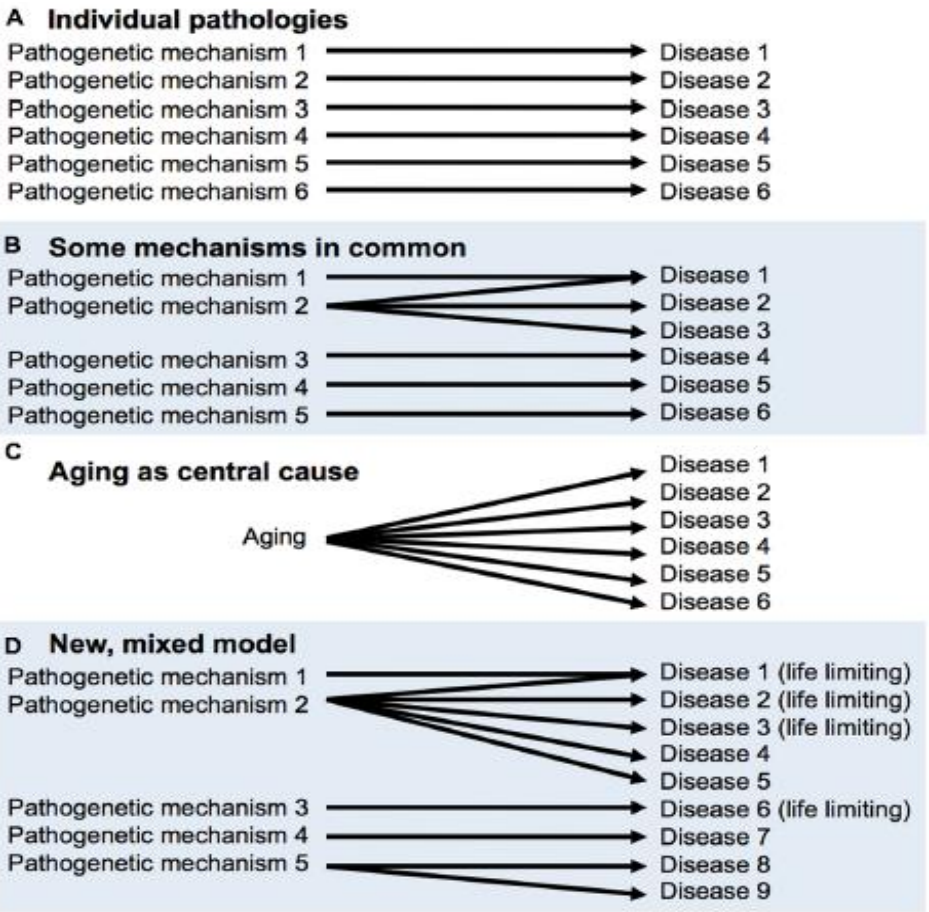
The aging-disease false dichotomy: understanding senescence as pathology

*David Gems**

Institute of Healthy Ageing and Department of Genetics, Evolution and Environment, University College London, London, UK



Big Questions in Aging

- **What are the biological mechanisms driving aging?**
- **Which candidate interventions work and why?**
- **From SICKcare to HEALTHcare?**

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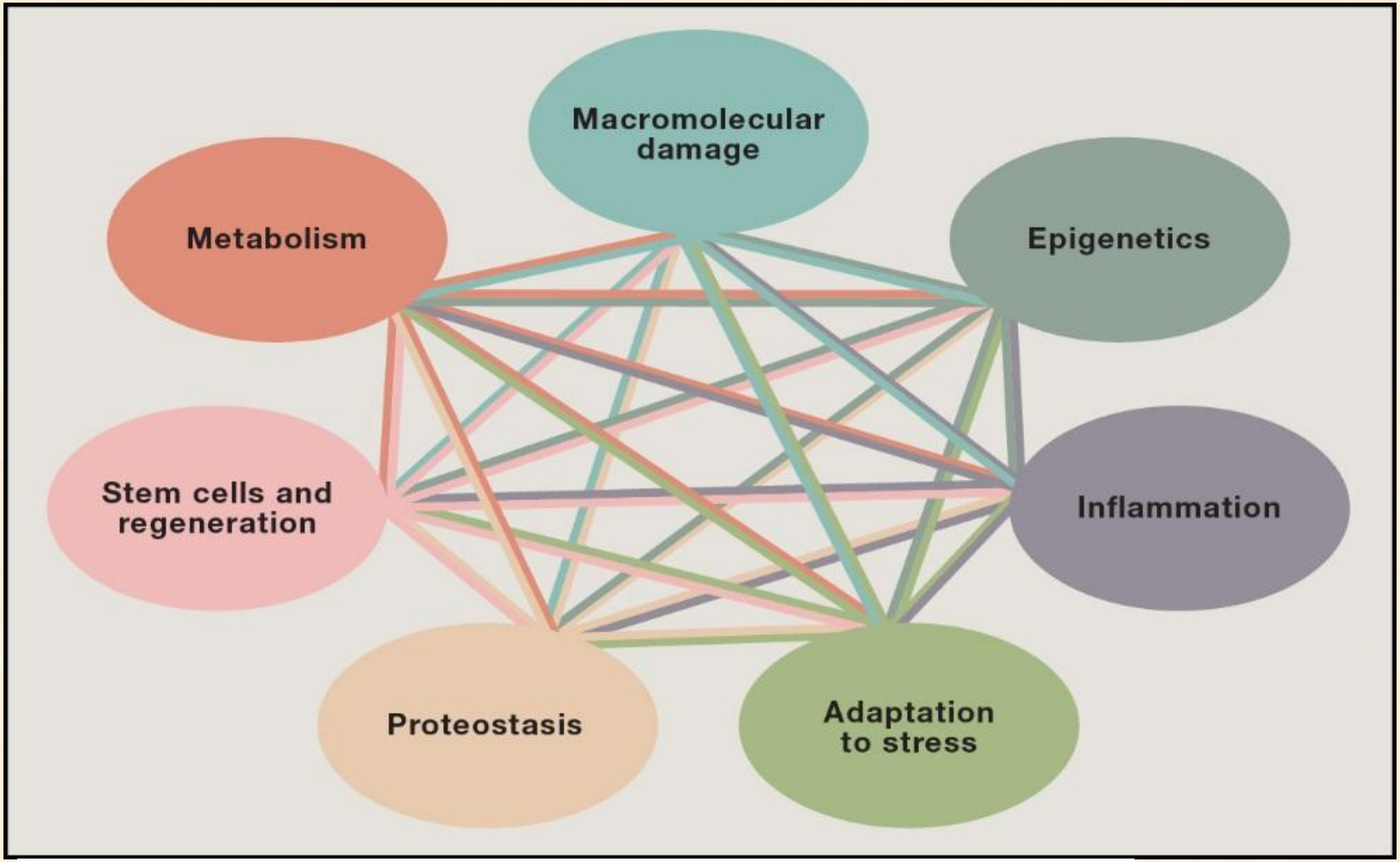
Biological Determinants of Aging



Geroscience: Linking Aging to Chronic Disease

Brian K. Kennedy,[1,*] Shelley L. Berger,[2,3] Anne Brunet,[4,5] Judith Campisi,[1,6] Ana Maria Cuervo,[7,8] Elissa S. Epel,[9] Claudio Franceschi,[10,11,12] Gordon J. Lithgow,[1] Richard I. Morimoto,[13] Jeffrey E. Pessin,[14] Thomas A. Rando,[5,15,16] Arlan Richardson,[17,18] Eric E. Schadt,[19] Tony Wyss-Coray,[15,16] and Felipe Sierra[20]

Cell

Big Questions in Aging

- What are the biological mechanisms driving aging?

- **Which candidate interventions work and why?**

- **From SICKcare to HEALTHcare?**

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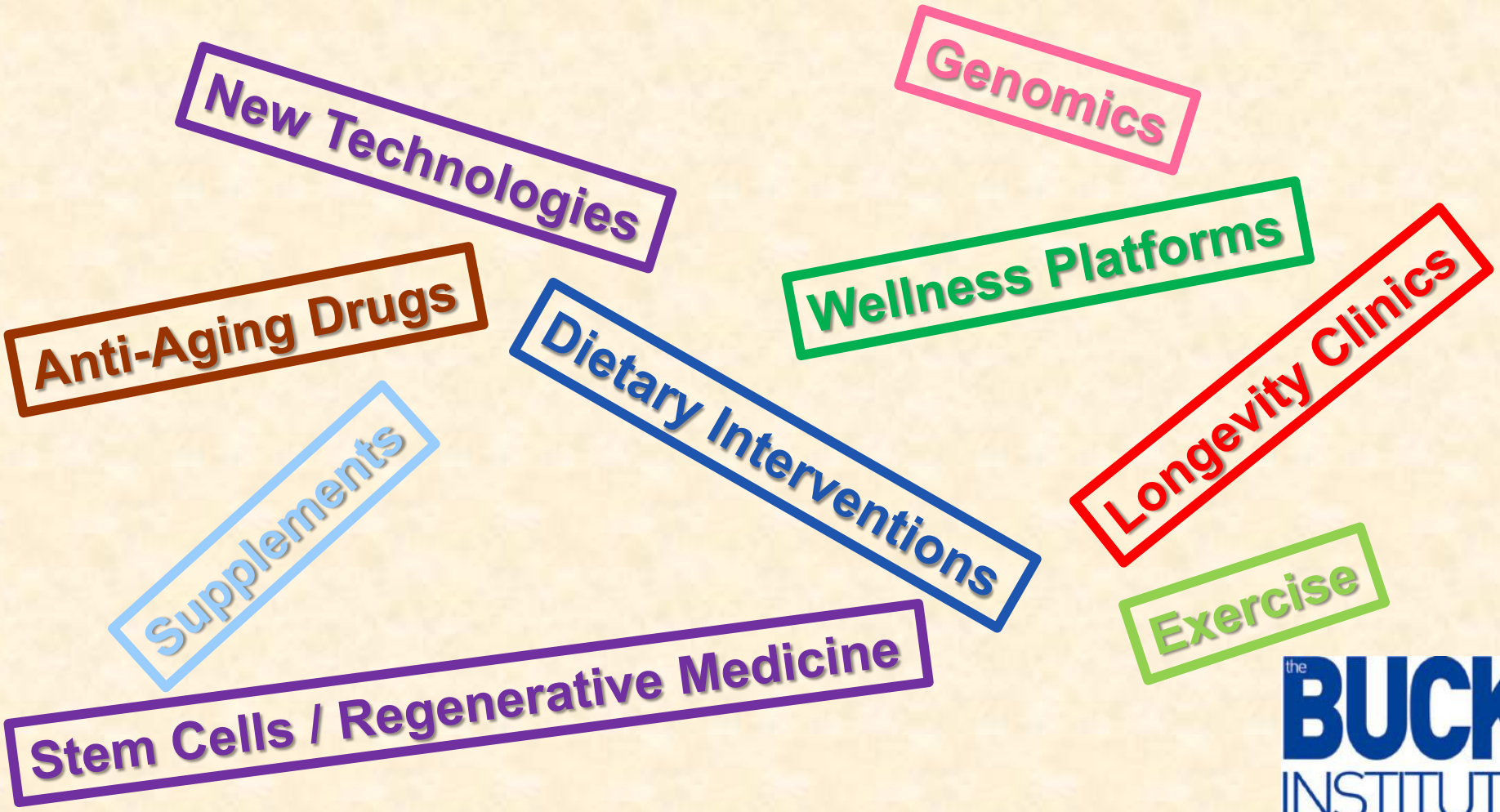
The Emergence of the Commercial Aging Field – BUYER BEWARE!



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Lifespan extension Agents

BEHAVIORAL

1. Calorie Restriction
2. Exercise
3. Intermittent Fasting
4. Alcohol??????

.
.
.

SMALL MOLECULES

1. Rapamycin
2. Metformin
3. NSAIDs
4. Acarbose
5. STACs (Resveratrol)

.
.
.

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Emerging Approaches

- **Nutritional Supplements**
  - **NAD Precursors**
  - **TCM**
- **Drug Development**
  - **Senolytics**
- **Gene Therapy**
  - **Telomere Extension**
- **Longevity Clinics**
- **Medical Diets**

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Clinical Testing in Humans

- **HEALTHSPAN Trial (Metformin)**
- **Treating age-related disease**
- **Testing against aging biomarkers**

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Possible Biomarkers

- Epigenetic Clock
- Metabolomics
- p16INK4A protein levels
- Inflammatory Markers
- Telomere length
- Functional markers (walking speed etc.)
- Systems Approaches

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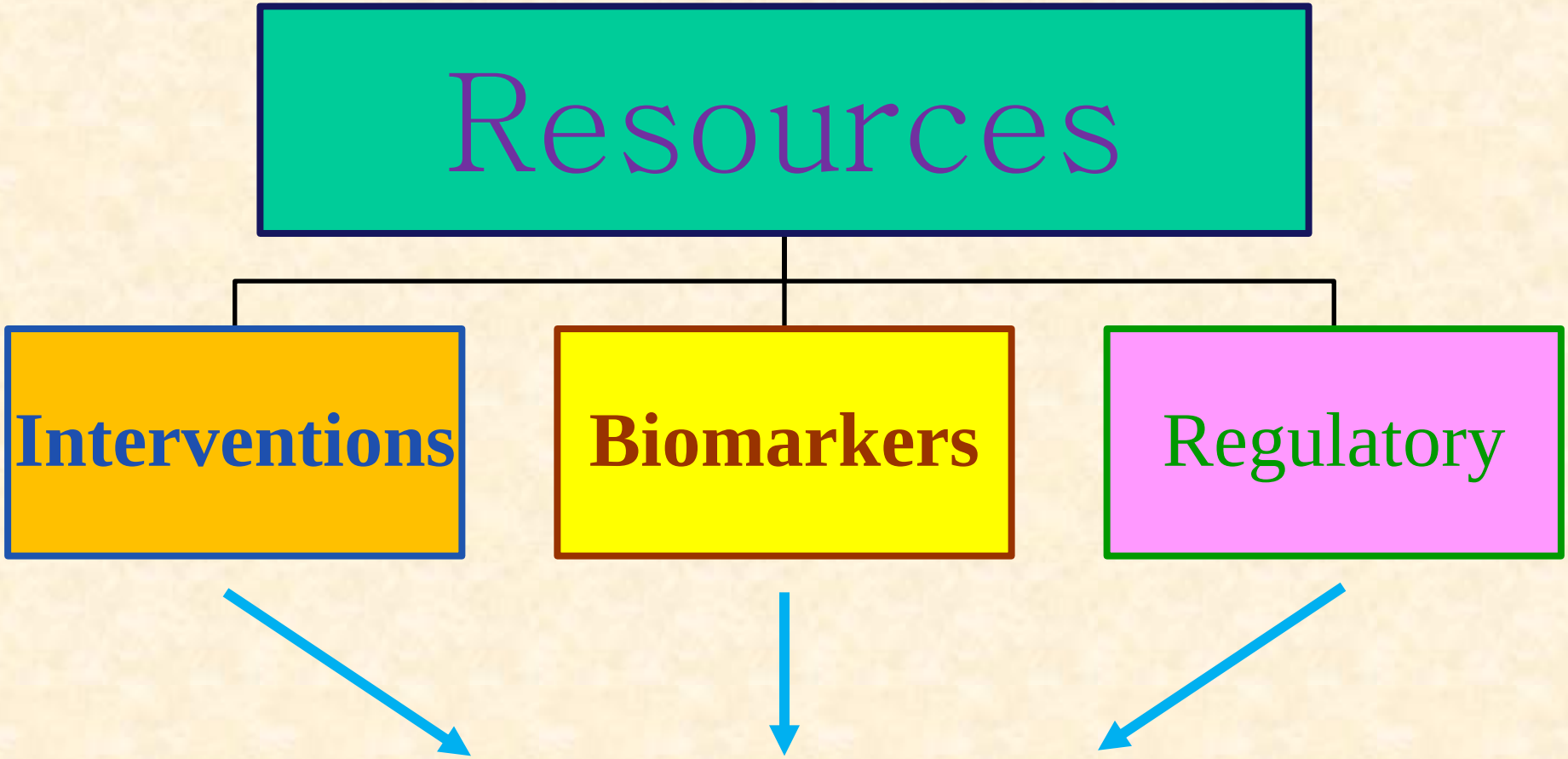
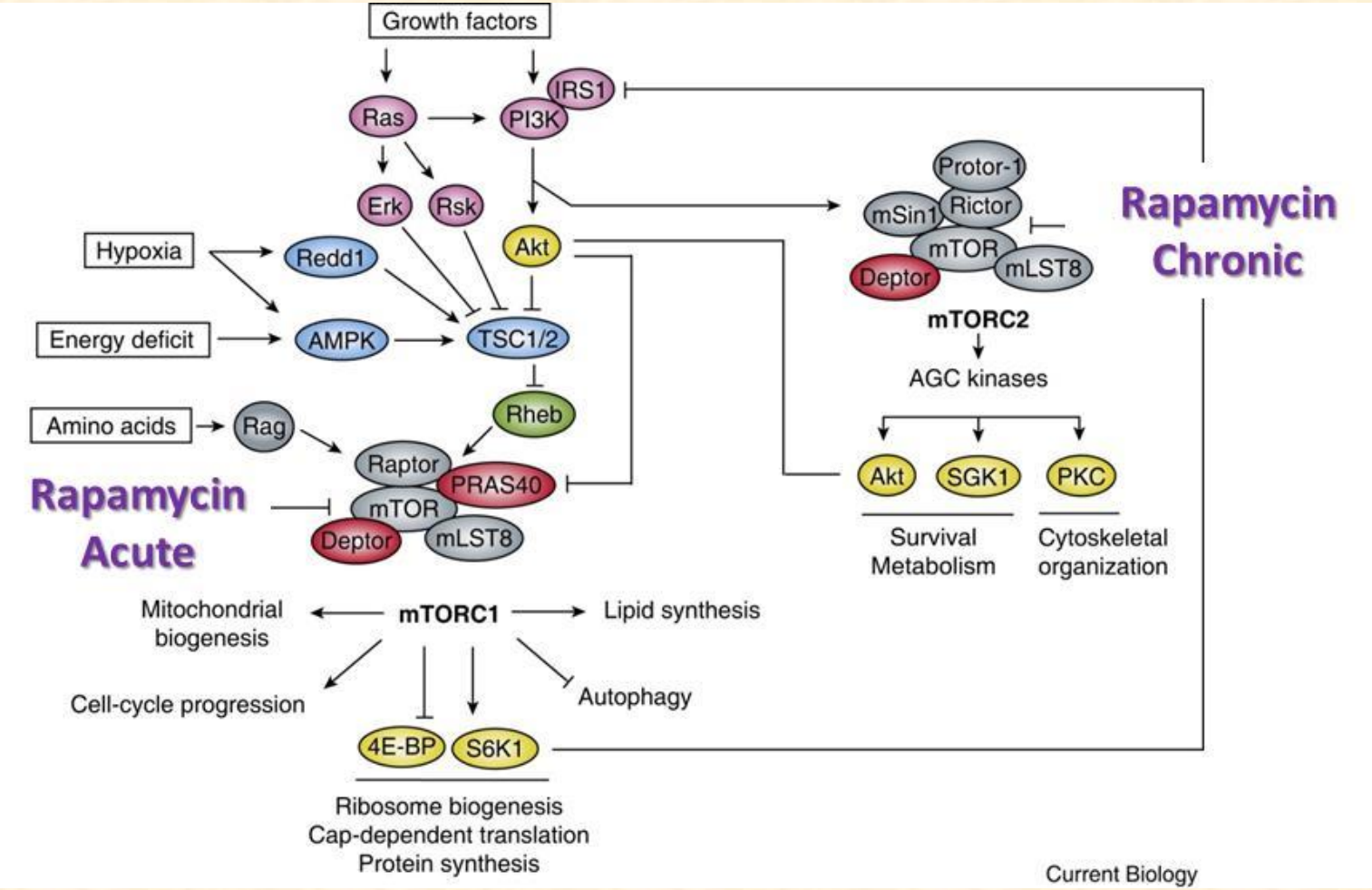


Longer, Healthier Lives

Rapamycin?



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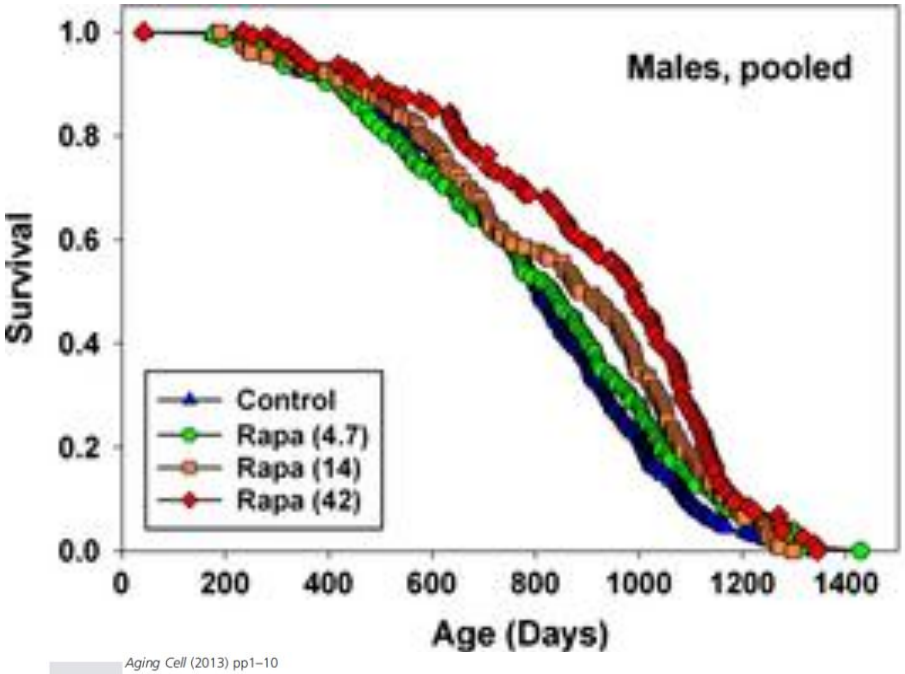
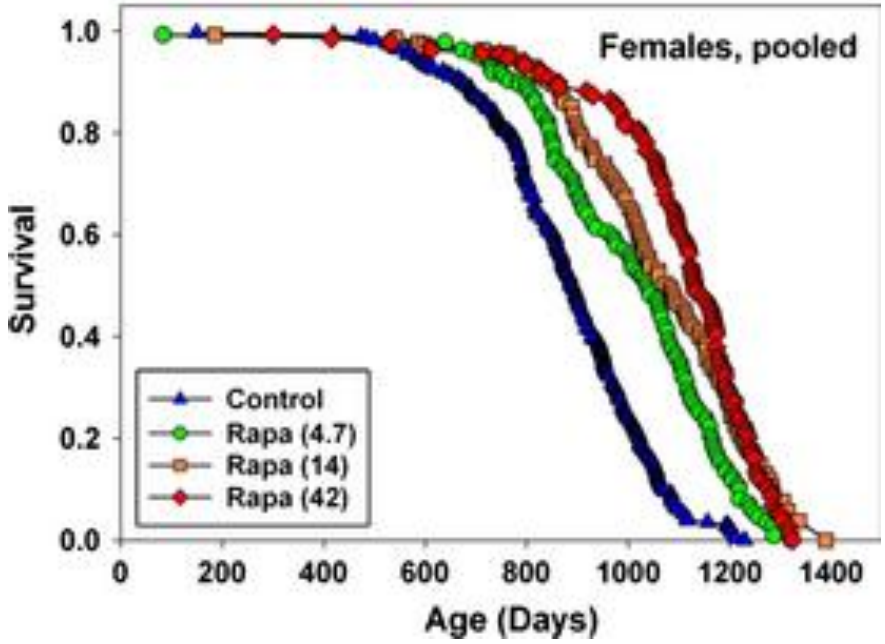
Rapamycin is dose dependent



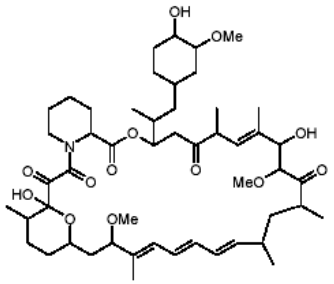


Aging Cell (2013) pp1–10

Doi: 10.1111/acel.12194

Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction

Richard A. Miller,[1]* David E. Harrison,[2]* Clinton M. Astle,[2] Elizabeth Fernandez,[3] Kevin Flurkey,[2] Melissa Han,[1] Martin A. Javors,[4] Xinna Li,[1] Nancy L. Nadon,[5] James F. Nelson,[6] Scott Pletcher,[7] Adam B. Salmon,[8] Zelton Dave Sharp,[8,9] Sabrina Van Roekel,[1] Lynn Winkleman[1] and Randy Strong[3,8]*



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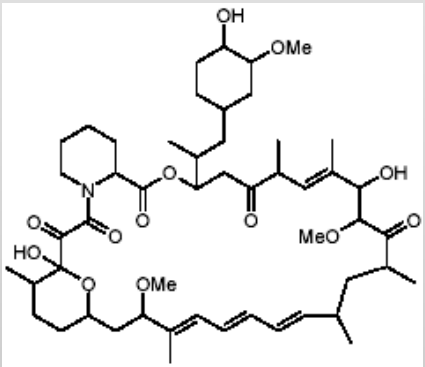
Rapamycin and Age-related Disease

雷帕霉素对多种衰老相关疾病有效

Neurodegeneration 神经退行性疾病（比如老年痴呆症）

Cancer 肿瘤

Frailty 虚弱



雷帕霉素

Stroke 中风

AMD 衰老导致的眼球黄斑退化

Type II Diabetes II型糖尿病

Arthritis 关节炎

Heart Disease 心脏疾病

Biochim. Biophys. Acta 1790: 1067-1074.

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Rapamycin – significant safety risks

雷帕霉素的使用有安全风险

- At doses relevant to disease treatment and lifespan extension, rapamycin has shown to 使用能够治疗疾病和延长寿命的雷帕霉素剂量导致各种代谢失调
  - Affect metabolism: Glucose intolerance, insulin resistance, glucose homeostasis
  - Present other side effects: lipid dysregulation, stomatitis
- Significantly limits therapeutic potential of rapamycin & analogs

这些副作用很大程度上限制了雷帕霉素以及类似物在临床上的应用

Table 1 mTOR inhibitors—summary of toxicities 表1：雷帕霉素副作用总结

Toxicity		Temsirolimus [1–3, 15, 24]		Everolimus [4, 5, 25]		Ridaforolimus [6, 7, 20]	
		All grades (%)	Gr 3/4 (%)	All grades (%)	Gr 3/4 (%)	All grades (%)	Gr 3/4 (%)
粘膜炎	Mucositis	20–75	1–4	40–44	3–4	45–78	15–16
皮疹	Skin rash	47–76	4	25–29	<1	48–66	2–3
肺损失	Pulmonary toxicity[a]	2–36	9	8–14	3–4	15	3
高血糖症	Hyperglycemia	26–89	17–16	50–57	12–15	22	6–13
高胆固醇	Hypercholesterolemia	21–87	1–21	76–77	3–4	28	0
高甘油三酯血症	Hypertriglyceridemia	21–83	3–4	71–73	<1	9–13	4
血磷酸盐过少症	Hypophospatemia	13–49	13–18	32–37	4–6	23	15
贫血症	Anemia	29–45	9–20	91–92	9–13	53	0
血小板减少症	Thrombocytopenia	14–40	1–8	20–23	1	18–22	6–15
白血球减少症	Neutropenia	7–19	3–5	11–14	0	7–19	3–4
虚弱无力	Asthenia/fatigue[b]	38–51	8–11	31–38	4–5	20–76	3–4
味觉障碍	Dysgeusia	20–21	0	7–10	0	26	0

[a] Reported as dyspnea in most trials. [b] Reported either as fatigue or asthenia

Soefje et al., Targ Oncol (2011) 6:125–129

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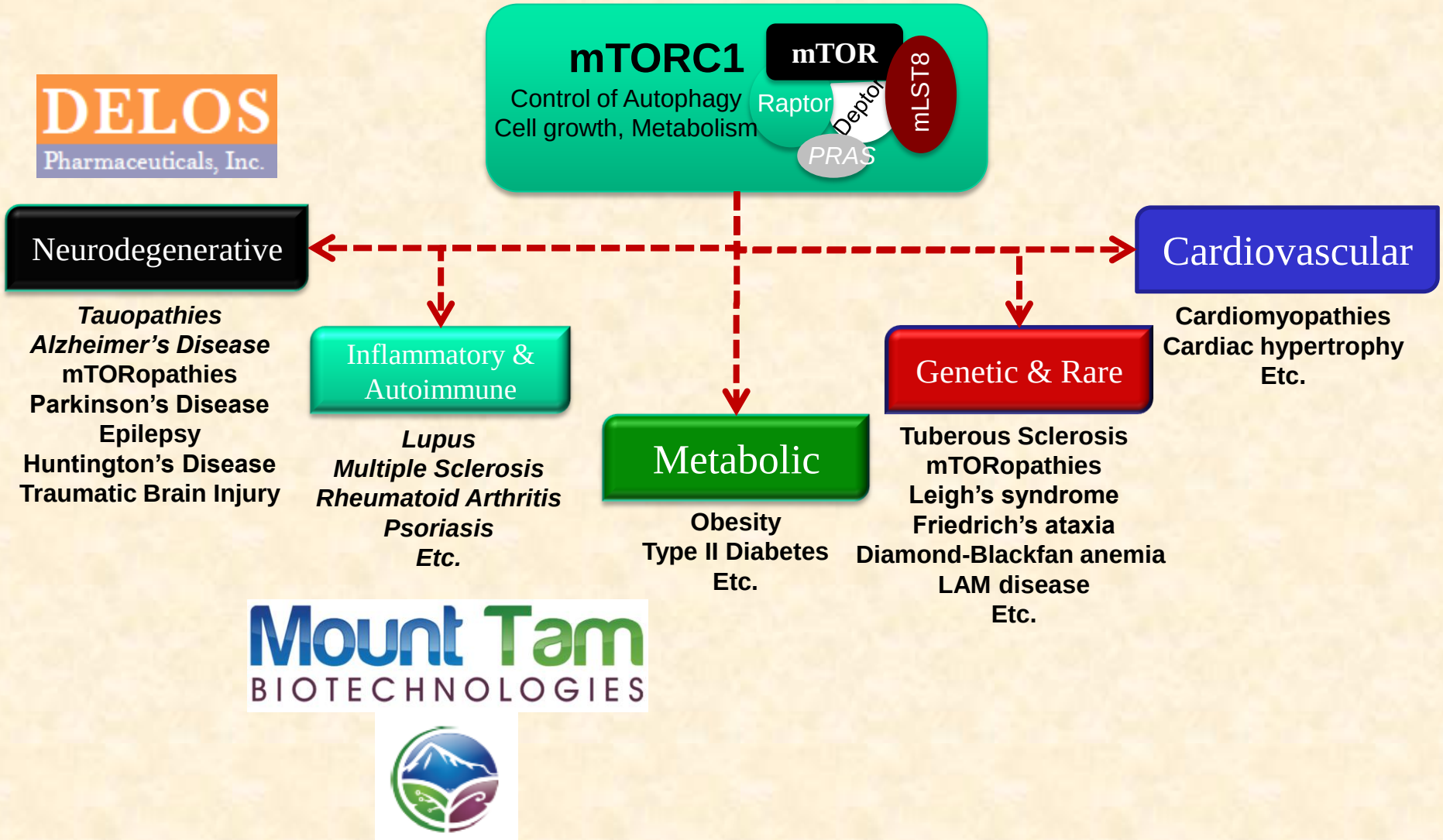
Trials in Dogs

Rapamycin trial in companion (pet) dogs

- Larger-breed dogs with average lifespan ~8-12 years
- Start **low dose** rapamycin at 6-9 years
  - Minimal if any side effects
- Follow healthspan parameters and survival in treated and untreated animals for 3-5 years
- Prediction: Treated animals will be healthier and have lower mortality than untreated animals

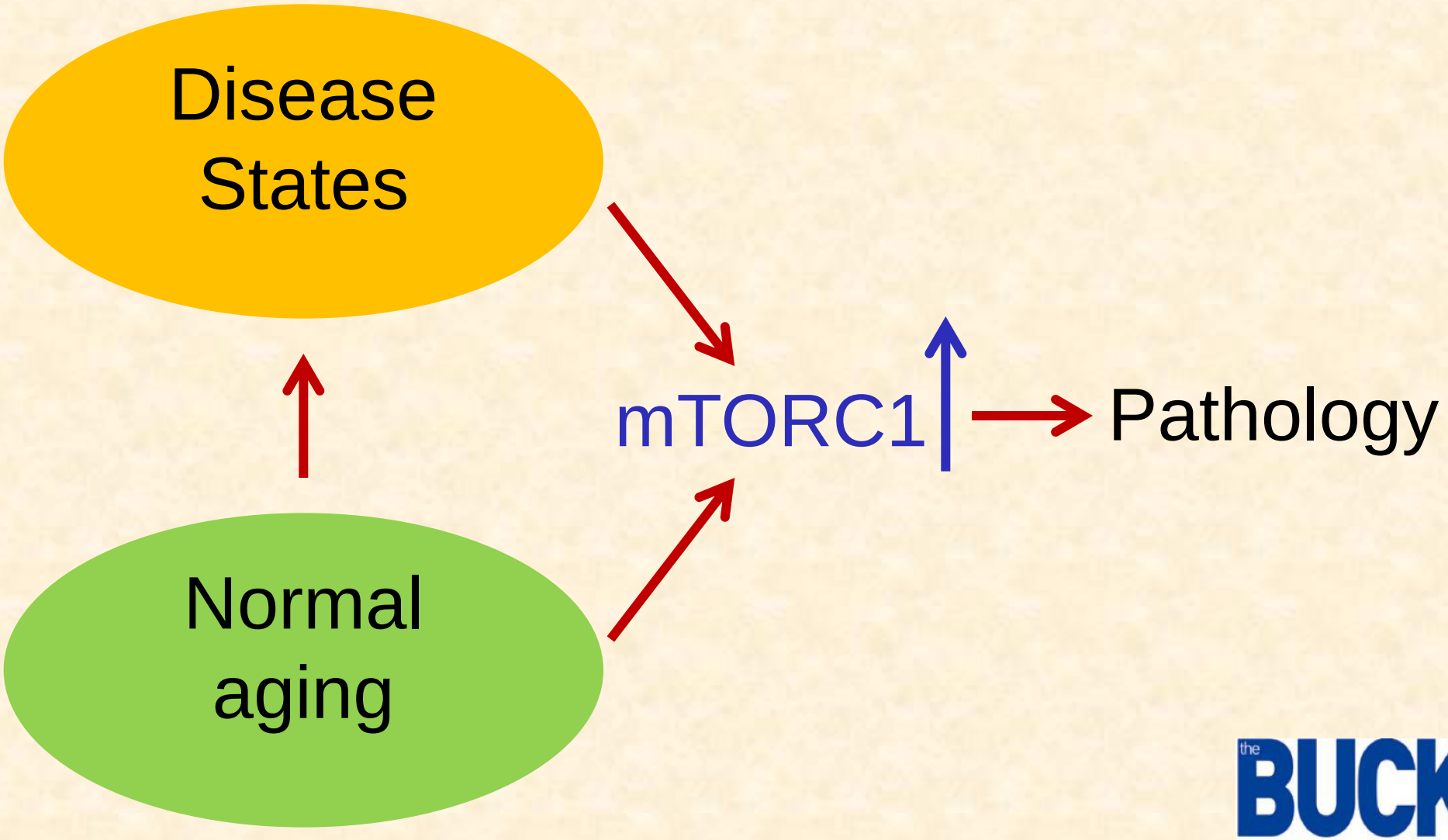
Many Potential Disease Indications



DELOS Pharmaceuticals, Inc.

Mount Tam BIOTECHNOLOGIES

Aberrant mTOR activation



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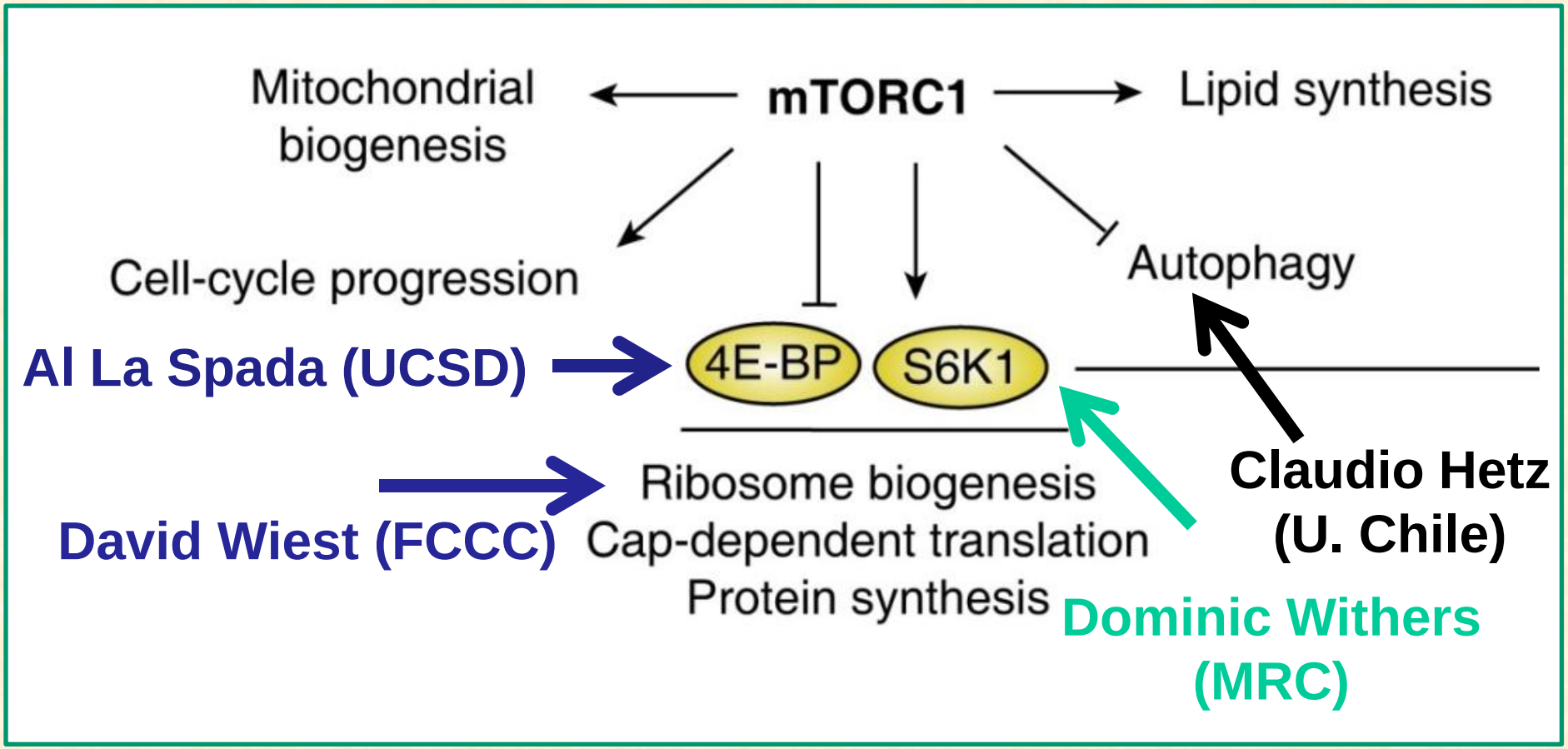
Downstream of TOR for Aging and Metabolism



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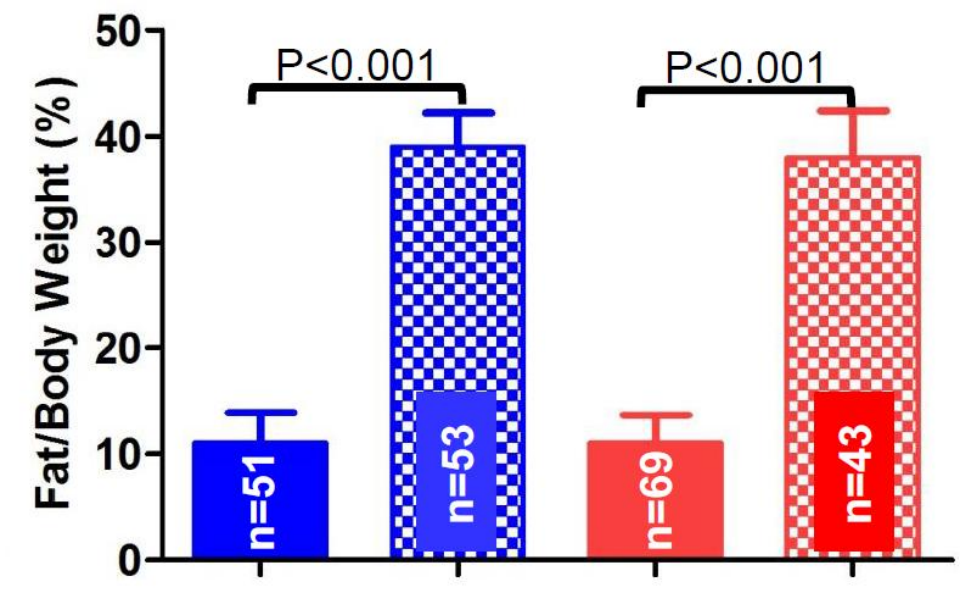
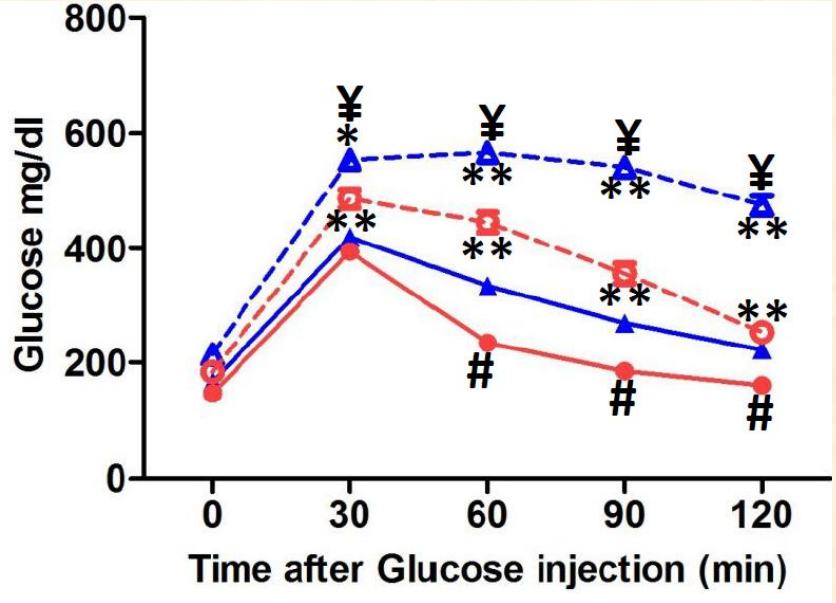
Males have Increased Diabetic Phenotypes at the Same Level of Obesity





Shihyin Tsai

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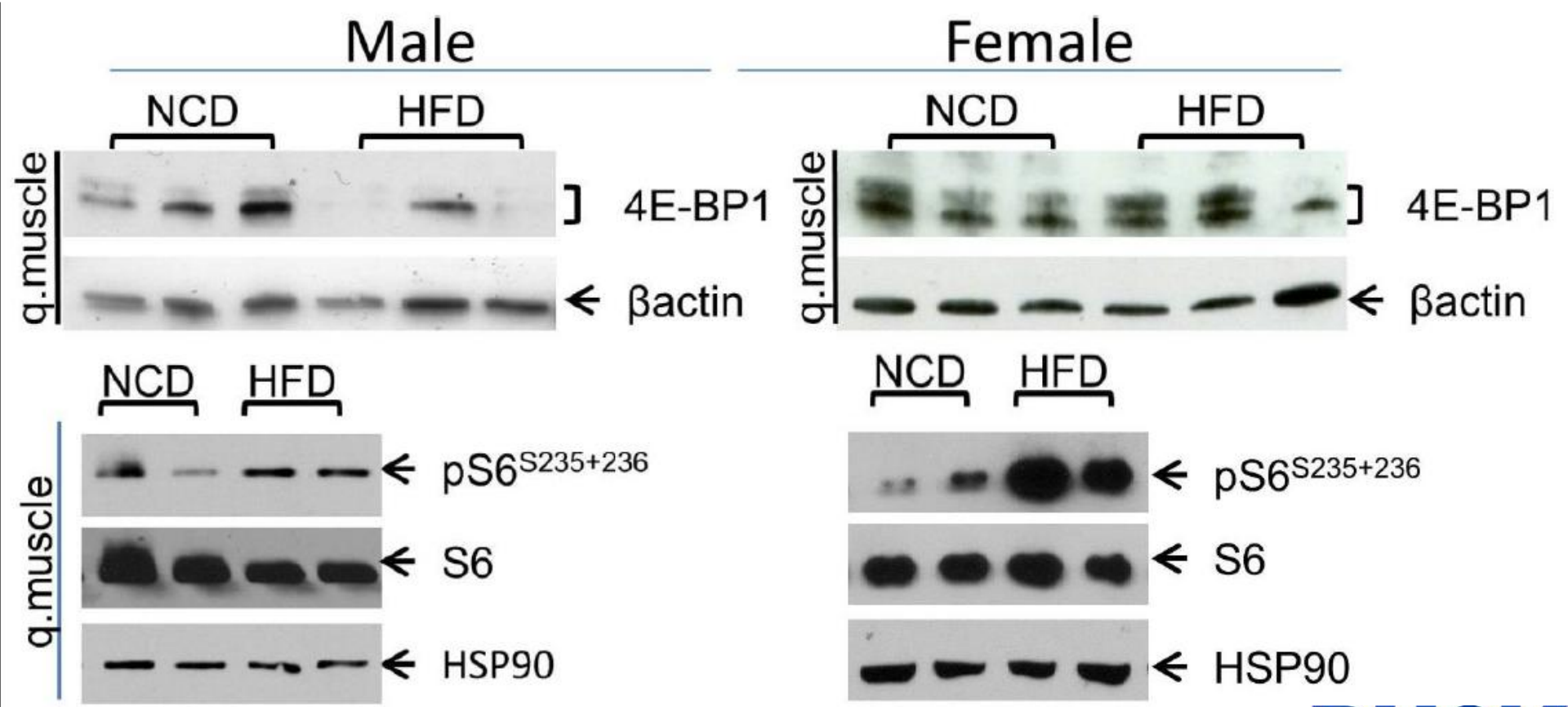
Loss of 4E-BP1 Specifically in Males



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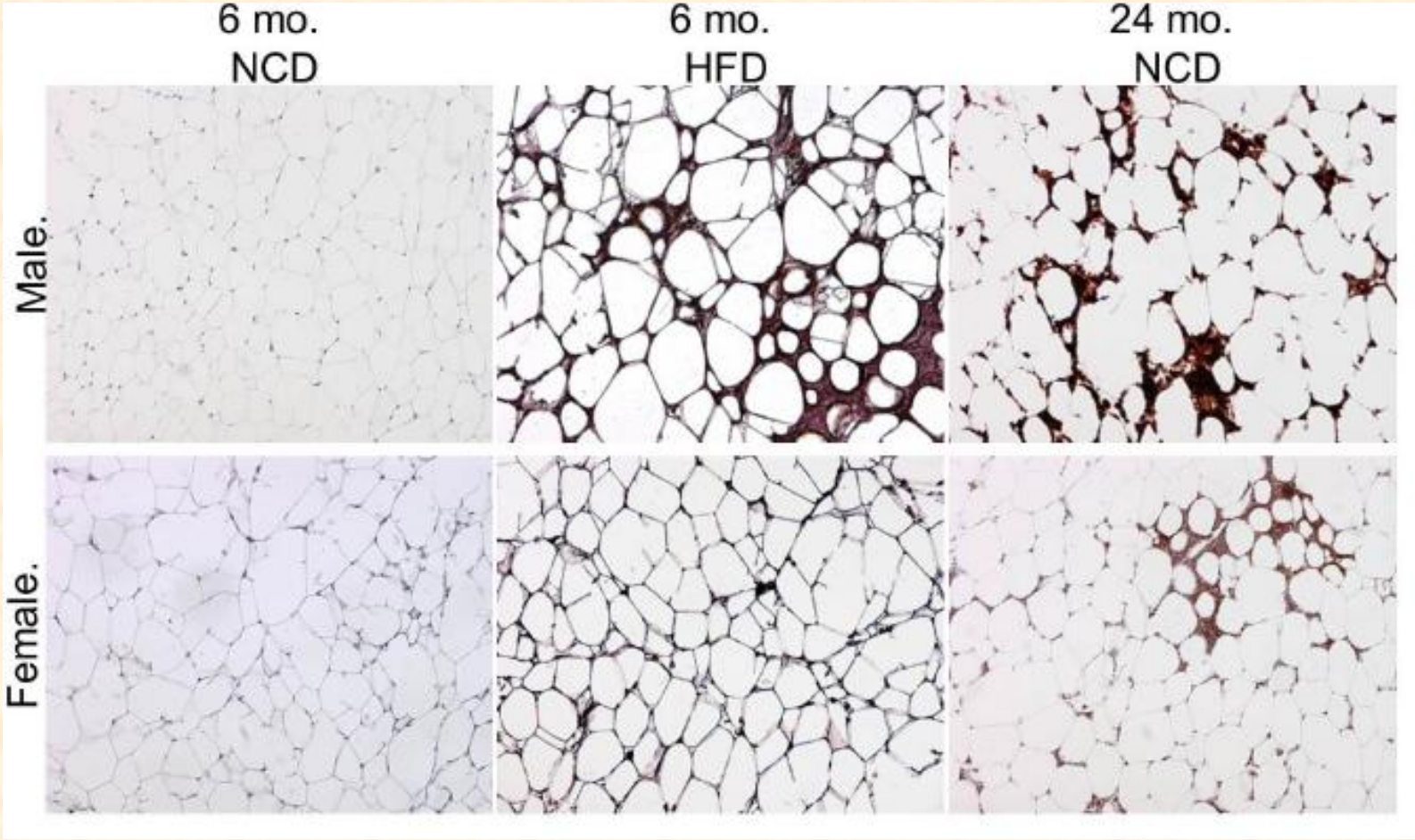
Males have Higher Levels of Inflammation



F4/80 Staining

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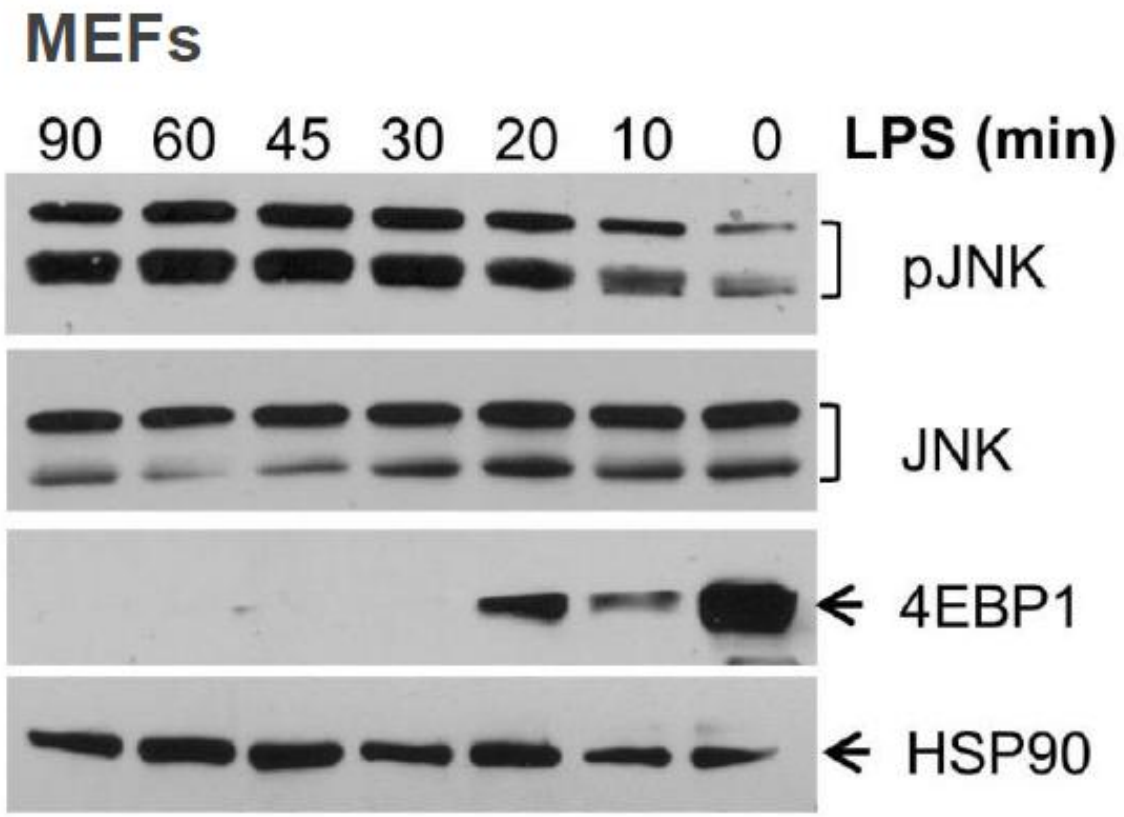
Inflammation Triggers Degradation of 4E-BP1



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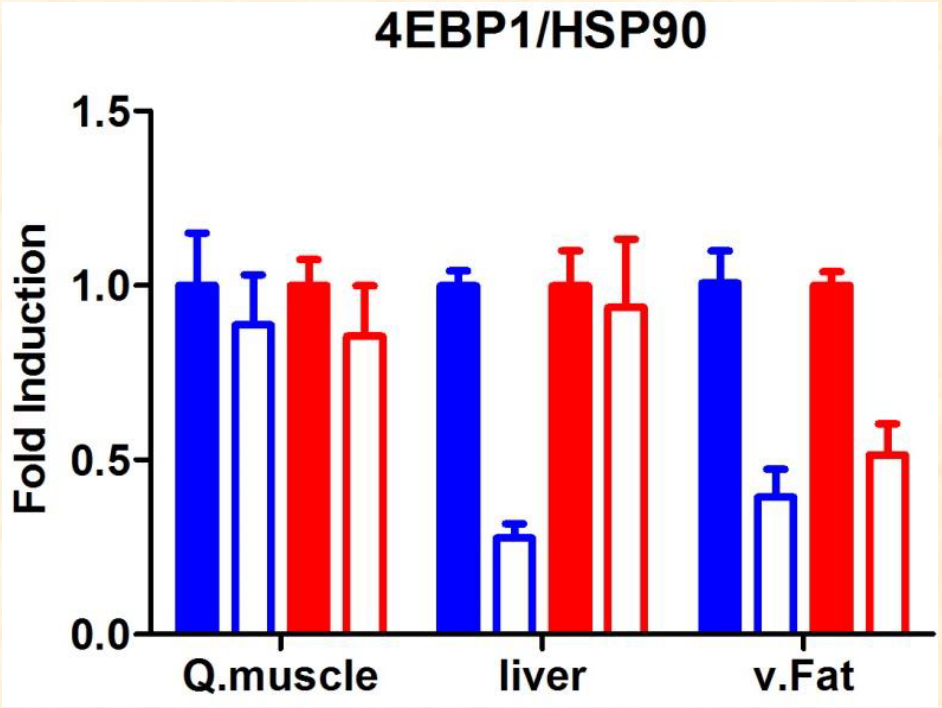
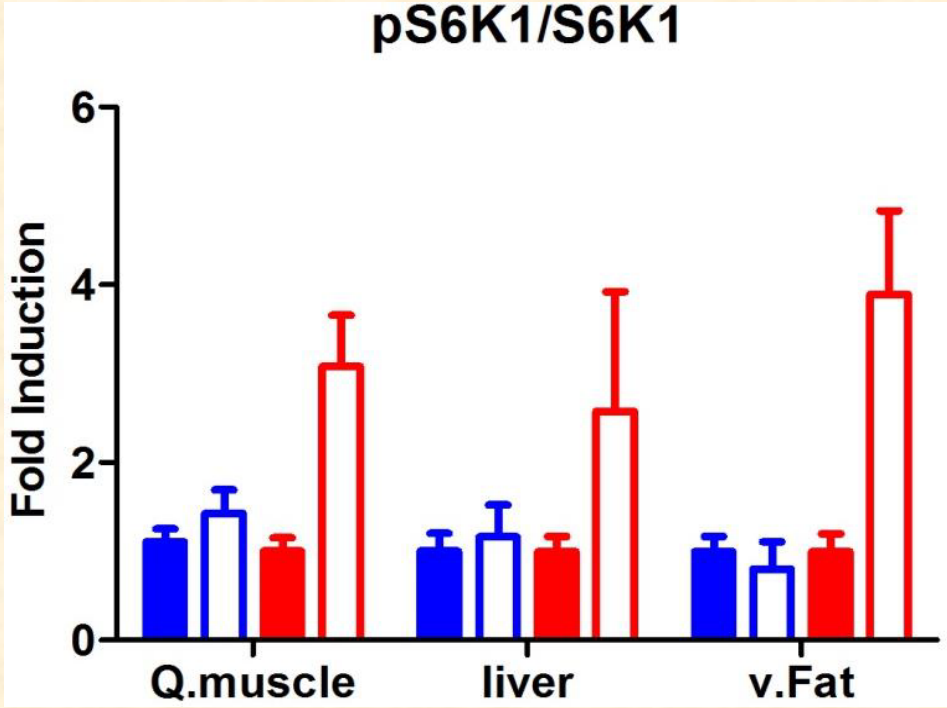
Altered 4E-BP1 Levels and S6K1 Phosphorylation with Age





Young-Male
Old-Male
Young-Female
Old-Female

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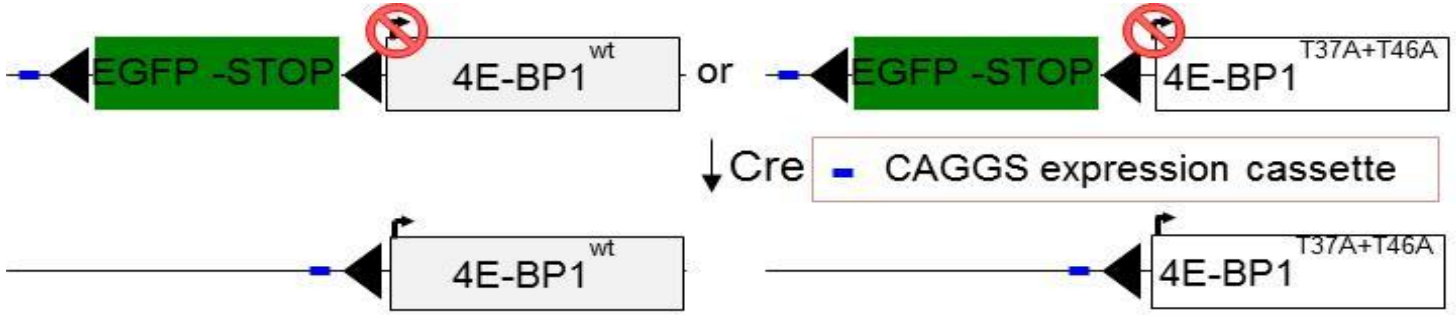
4E-BP1 Transgenic Mice



Expression	4E-BP1 WT	4E-BP1 Mut
Whole Body	Small	Lethal
Adipose	Normal	Obese
Skeletal Muscle	Normal	Small
Liver	Ongoing	Ongoing

The Journal of Clinical Investigation

RESEARCH ARTICLE

Muscle-specific 4E-BP1 signaling activation improves metabolic parameters during aging and obesity

Shihyin Tsai,[1] Joanna M. Sitzmann,[1] Somasish G. Dastidar,[2] Ariana A. Rodriguez,[1] Stephanie L. Vu,[1] Circe E. McDonald,[1] Emmeline C. Academia,[1] Monique N. O'Leary,[1] Travis D. Ashe,[2] Albert R. La Spada,[2,3] and Brian K. Kennedy[1]

Al La Spada (UCSD)

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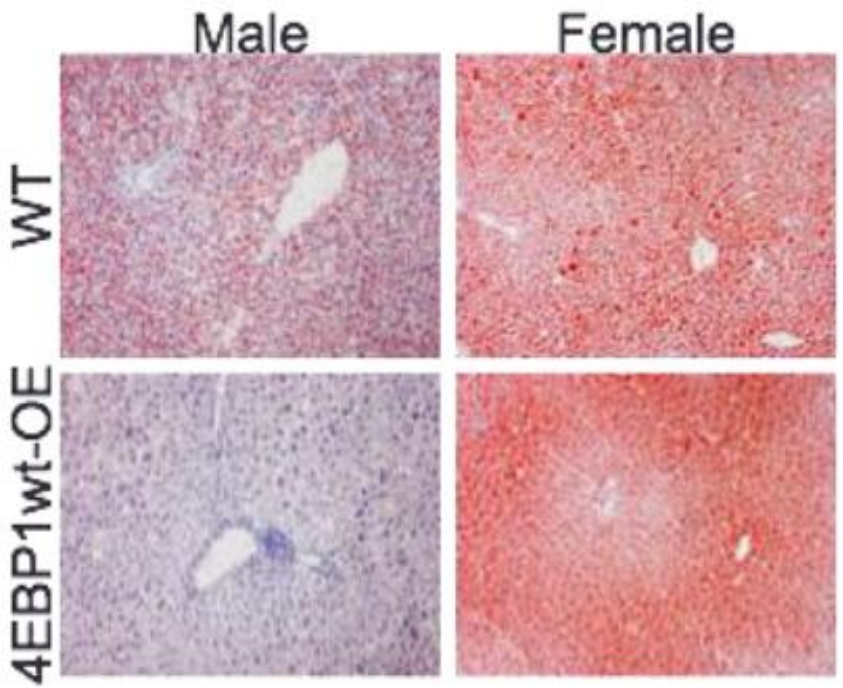
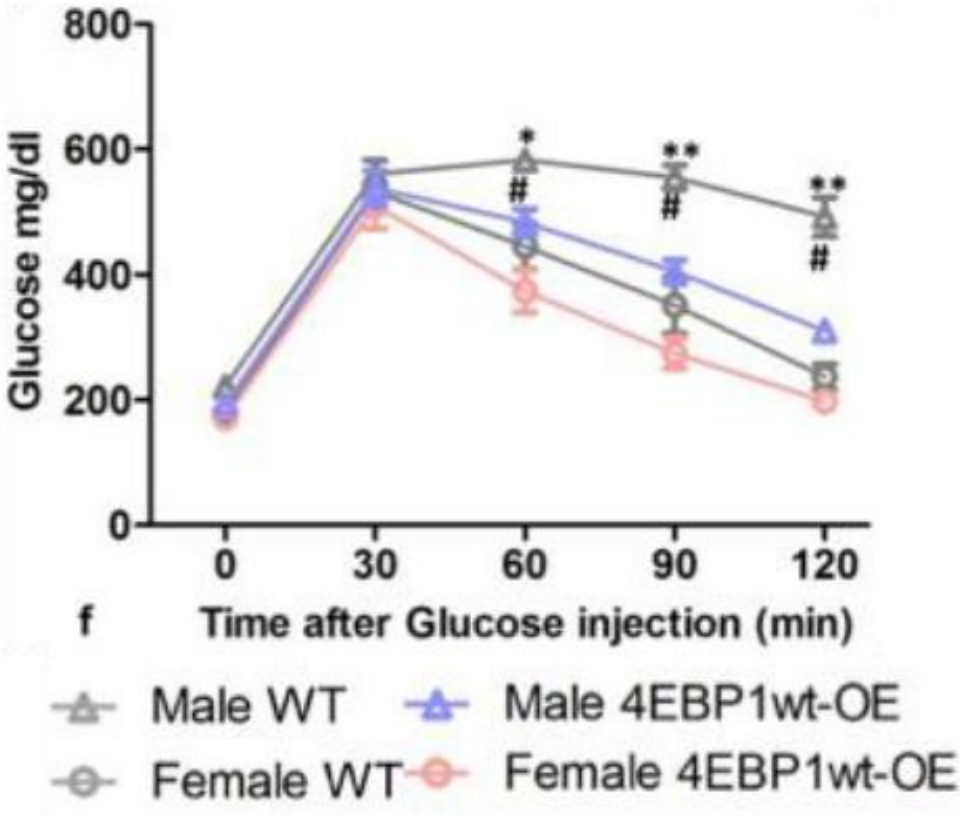
Overexpression of 4E-BP1 Protects Male Mice from Metabolic Dysfunction



Fatty liver



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Summary

- Inflammation Causes Loss of 4E-BP1

- Male Mice Resistant to Diabetes during a High Fat Diet (like females)

- Male Mice Protected from aging
  - Muscle Maintenance
  - Better Metabolism
  - Less Inflammation

Shihyin Tsai

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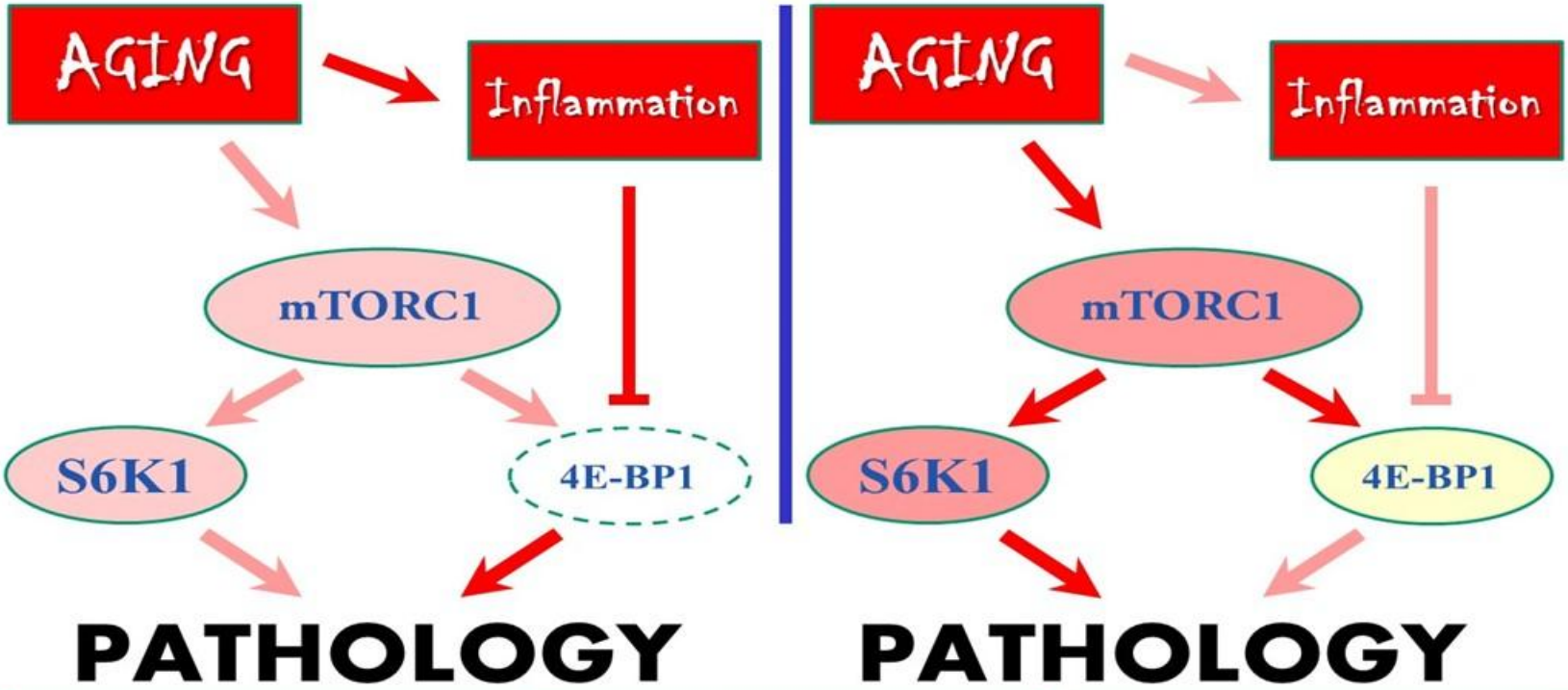
MALES

FEMALES



Lifespan extension?	MALES	FEMALES
Rapamycin	Yes	Yes
S6K1$^{-/-}$	No	Yes
4E-BP1Tg	Yes?	No?
Aspirin	Yes	No
17α-Estradiol	Yes	No

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Stuart Adamson
Regina Brunauer
Ningyuan Chen
Chong He
Yueh-Mei Hsu
Maria Konovalenko
Chen-Yu Liao
Mark McCormick
Bhumil Patel
Juniper Pennypacker
Christine Robbins
Shih-Yin Tsai
Junying Wang

Former Lab Members

Monique O'Leary (U Mich.)
Fresnida Ramos
Katherine Schreiber (Mt. Holyoke)

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Matt Kaeberlein, Peter Rabinovitch (UW), Alexey Moskalev (Skytyvkar State Univ.)
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Zhongjun Zhou (HKU), Shelley Berger (Penn), Yousin Suh, Marion Schmidt (AECOM)