

Developmental Biology

Lei Xue

Aging

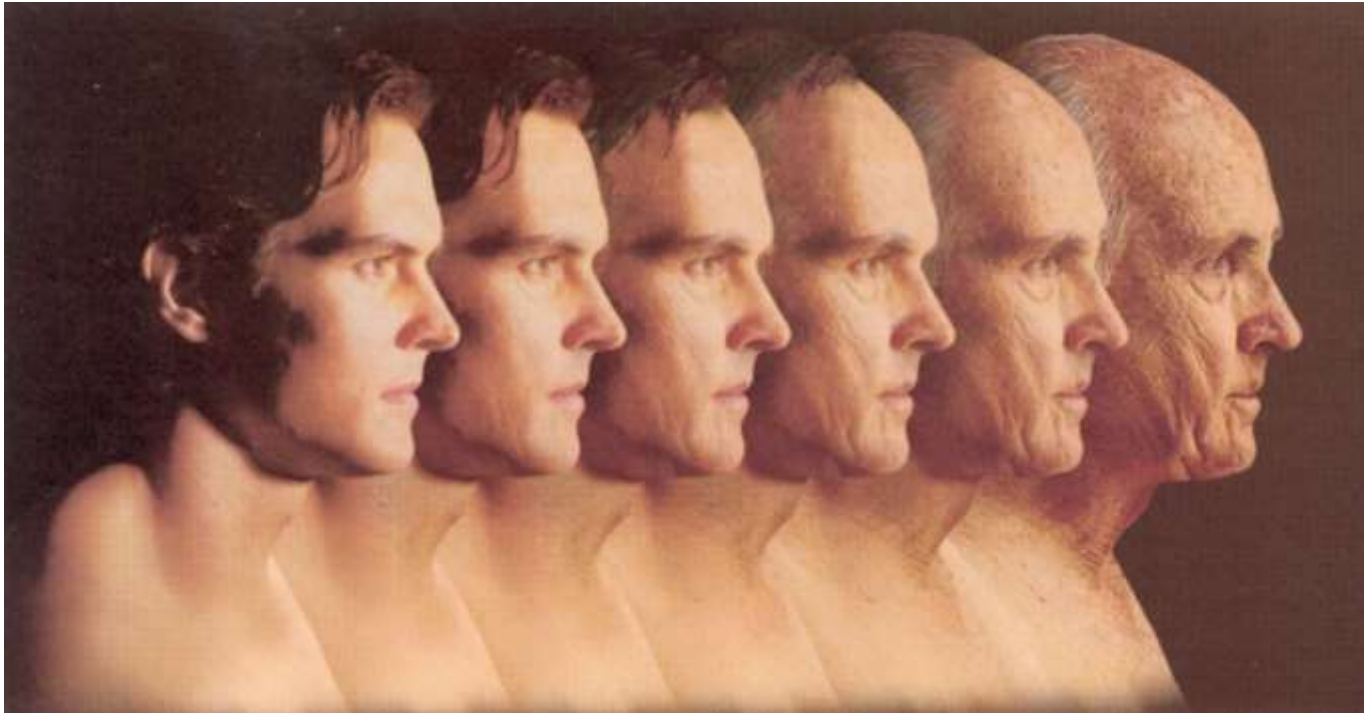
Cloning

Stem cell

壽

Aging (衰老)

The accumulation of changes in an organism over time



Aging theories:

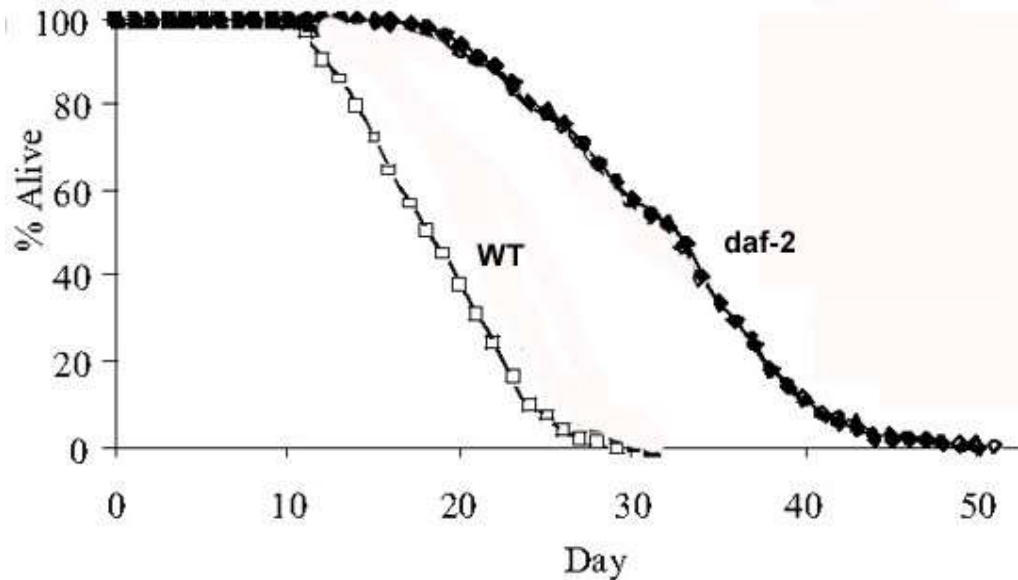
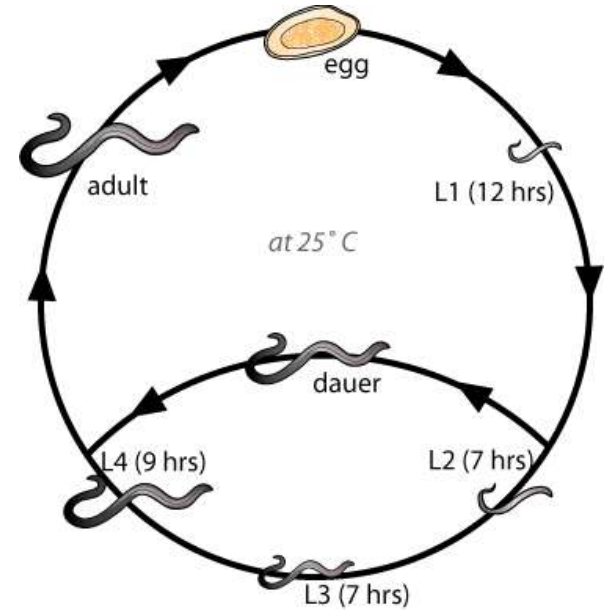
1. Genetics

- Insulin (胰岛素) signaling pathway

Genetic control of Lifespan



Cynthia Kenyon



daf2 = Insulin receptor
(胰岛素受体)

Insulin pathway

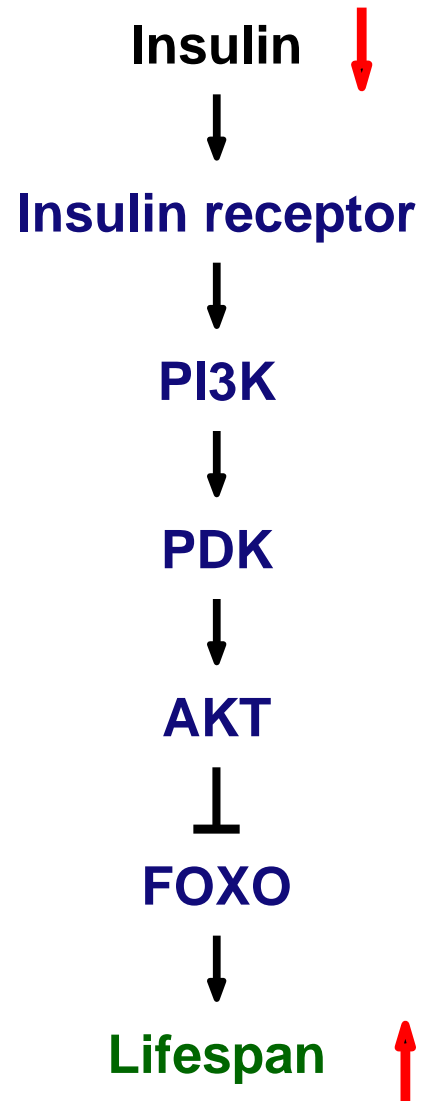
C. elegans



Drosophila



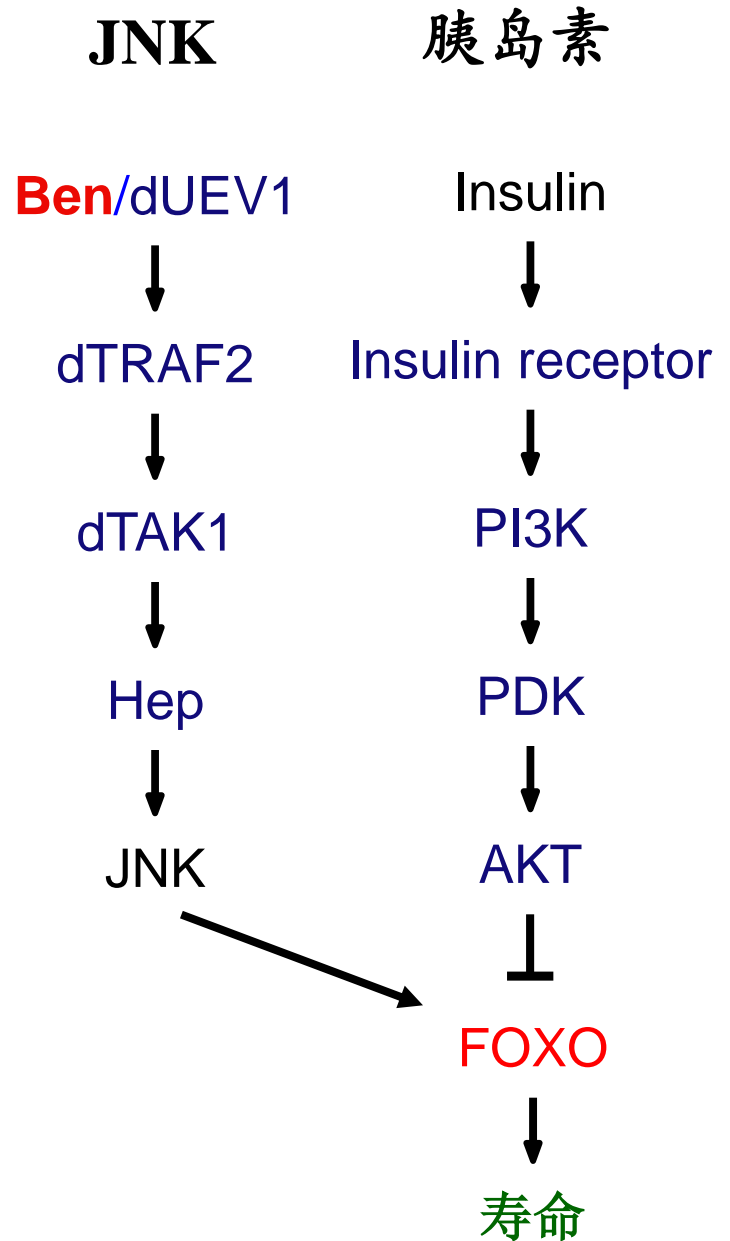
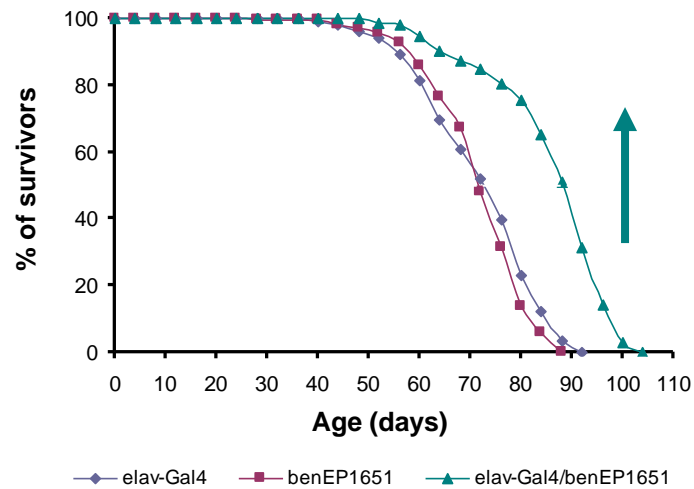
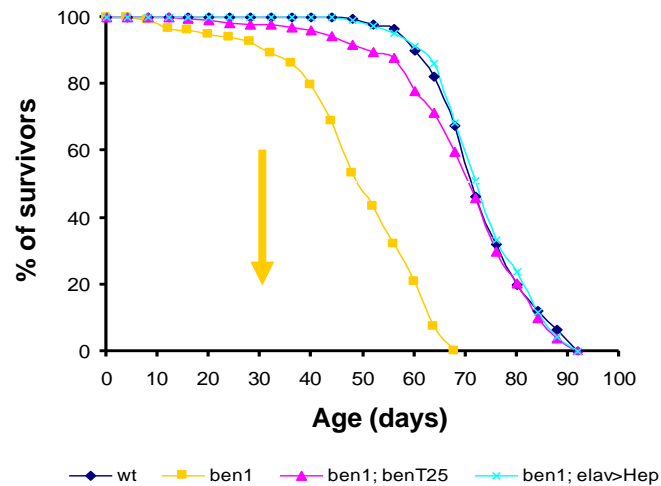
Mouse



Aging theories:

1. Genetics

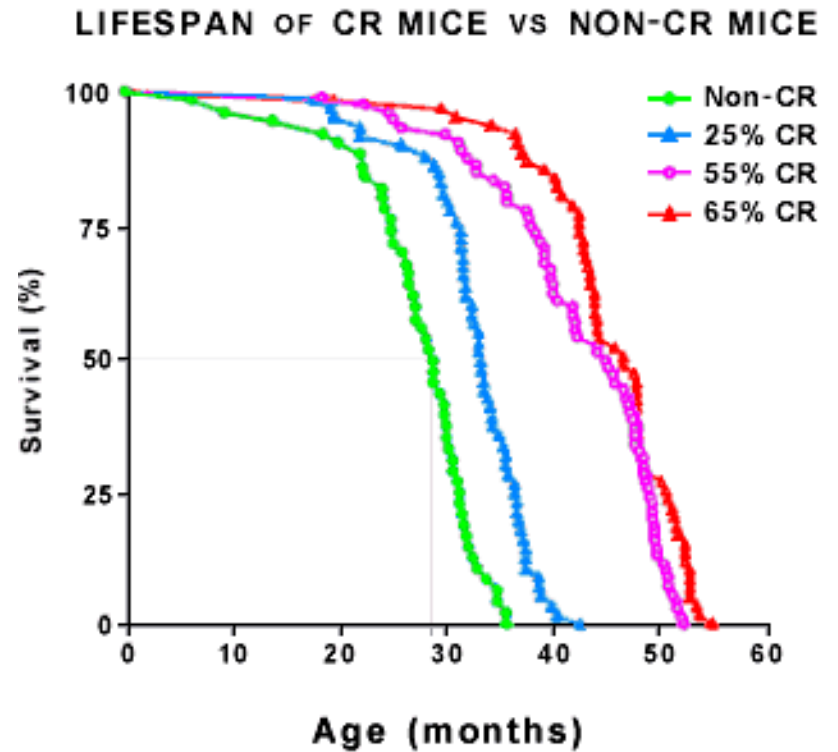
- Insulin (胰岛素) signaling pathway
- JNK signaling pathway



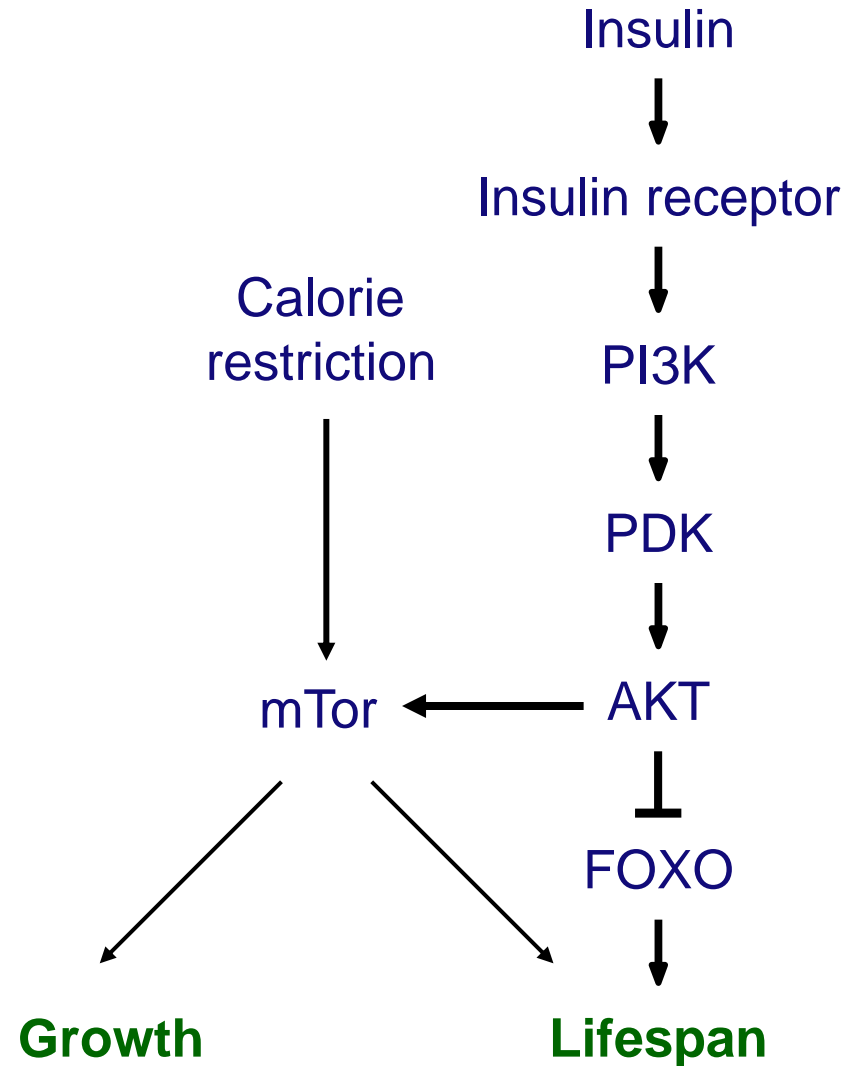
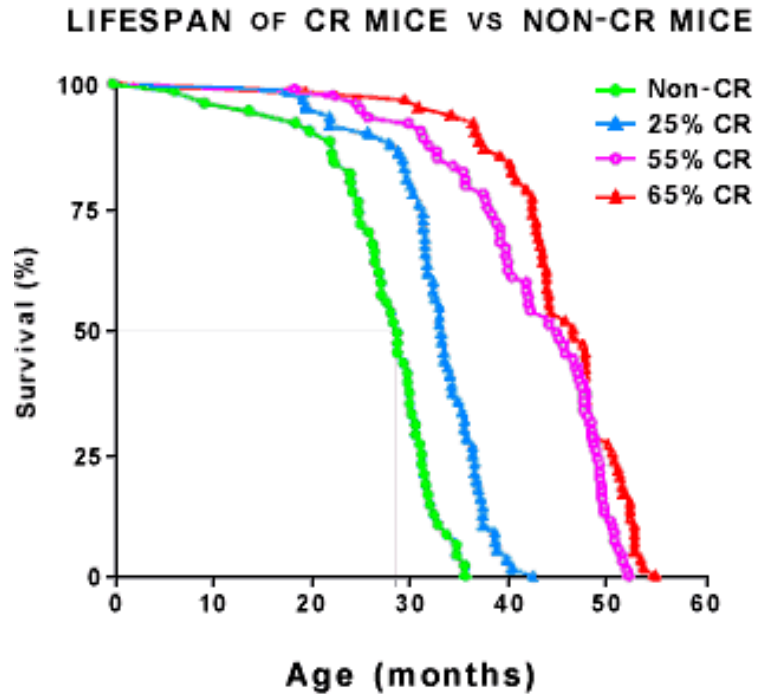
衰老的机制:

1. 遗传

2. 饮食限制 (CR)



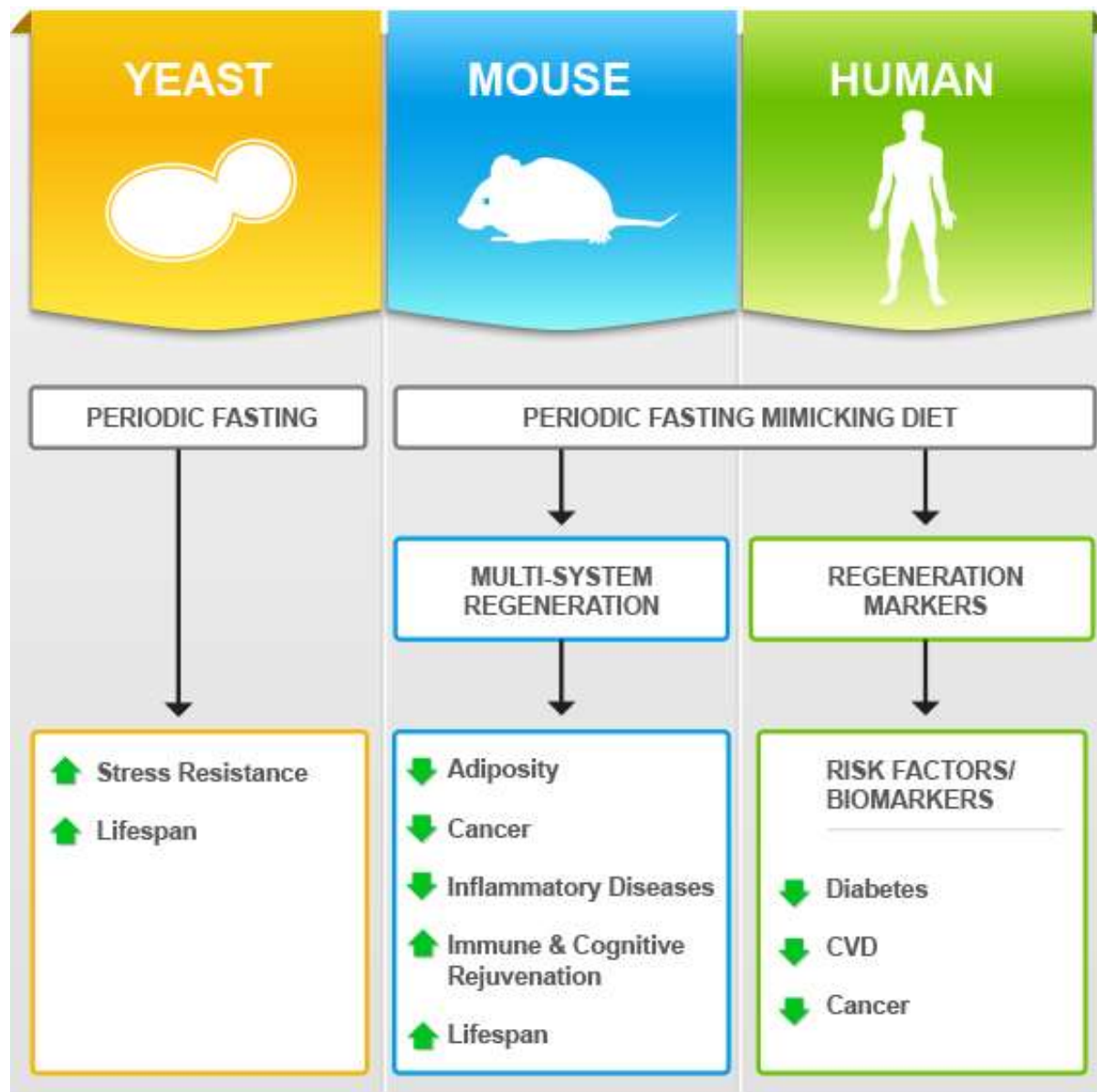
Calorie restriction



衰老的机制:

1. 遗传

2. 饮食限制 (CR)



THE
5:2

DIET BOOK

THE PART-TIME DIET
WITH *LIFE-CHANGING* RESULTS!



The **5:2 diet** is a **fasting diet plan**
limits the calorie intake for 2 days
eating 'normally' for the other 5 days per week



SHARE**RESEARCH ARTICLE** | METABOLIC DISEASE

Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease

Min Wei^{1,*}, Sebastian Brandhorst^{1,*}, Mahshid Shelehchi¹, Hamed Mirzaei¹, Chia Wei Cheng¹, Julia...

+ See all authors and affiliations

Science Translational Medicine 15 Feb 2017:
Vol. 9, Issue 377, eaai8700
DOI: 10.1126/scitranslmed.aai8700



Peer Reviewed
← see details

FMD: low in calories, sugars, and protein but high in unsaturated fats

71 healthy people, 5 days FMD /month for 3 months

body weight and total body fat

total and low-density lipoprotein cholesterol

insulin-like growth factor 1 (IGF-1)

blood pressure

C-reactive protein



hungry



ARTICLE

System-wide Benefits of Intermeal Fasting by Autophagy

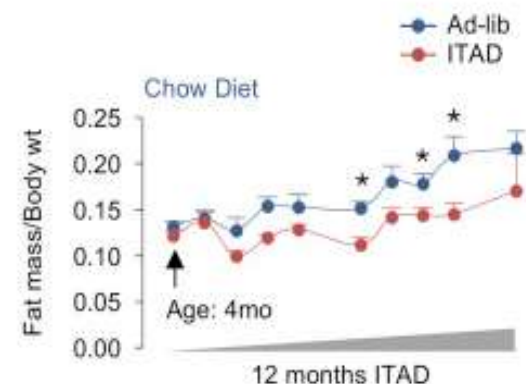
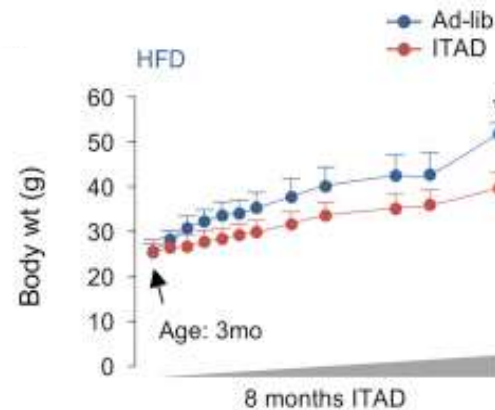
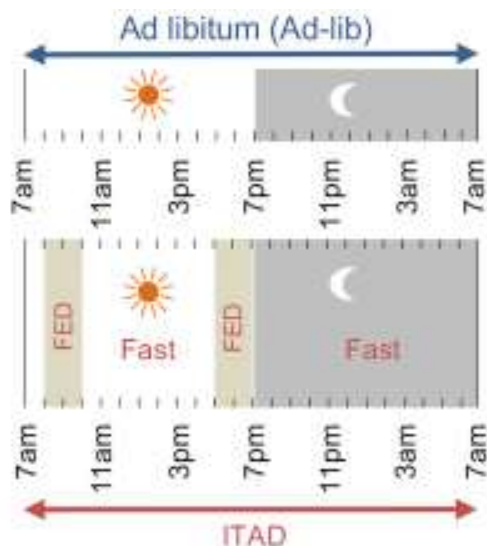
Nuria Martinez-Lopez^{7,8}, Elena Tarabra⁷, Miriam Toledo, Marina Garcia-Macia⁸, Srabani Sahu, Luisa Coletto, Ana Batista-Gonzalez, Nir Barzilai, Jeffrey E. Pessin, Gary J. Schwartz, Sander Kersten, Rajat Singh

⁷ These authors contributed equally

⁸ Present address: Institute for Cell and Molecular Biosciences, Newcastle University, Newcastle Upon Tyne NE4 5PL, UK


Publication stage: In Press Corrected Proof

Isocaloric twice-a-day (ITAD) : 一日两餐相等热量



ARTICLE

System-wide Benefits of Intermeal Fasting by Autophagy

Nuria Martinez-Lopez^{7,8}, Elena Tarabra⁷, Miriam Toledo, Marina Garcia-Macia⁸, Srabani Sahu, Luisa Coletto, Ana Batista-Gonzalez, Nir Barzilai, Jeffrey E. Pessin, Gary J. Schwartz, Sander Kersten, Rajat Singh  

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Publication stage: In Press Corrected Proof

Isocaloric twice-a-day (ITAD) : 一日两餐相等热量

ITAD feeding impacts autophagy in multiple tissues

ITAD feeding promotes diverse metabolic benefits in multiple tissue systems

ITAD feeding prevents age- and obesity-associated metabolic defects

Tissue-specific autophagy contributes to distinct benefits of ITAD feeding

consuming two meals a day without CR prevents metabolic syndromes

Aging theories:

1. Genetics

- Insulin (胰岛素) signaling pathway
- JNK signaling pathway

2. Calorie restriction (CR)

3. Free-radical (自由基) damage

- oxidative damage from reactive oxygen species (O_2^-)

Anti-oxidants

- CAT: Catalase (过氧化氢酶)
- SOD: Superoxide dismutases (超氧化物歧化酶)
- Vitamin E

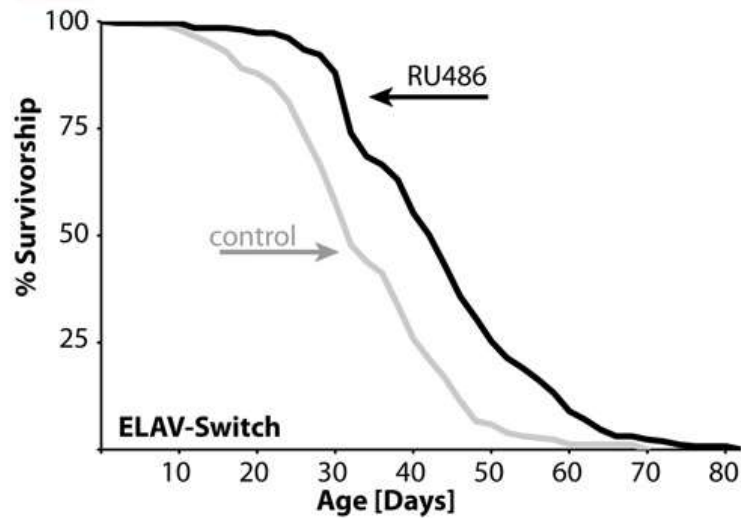


Pro-oxidants

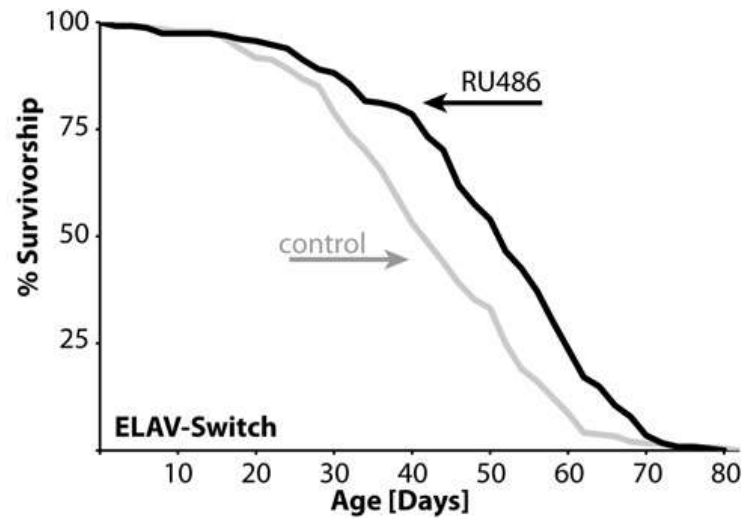
- Oxygen consumption
- Metabolism
- Physical exercise



Over-expression of CAT and SOD increase lifespan in *Drosophila*

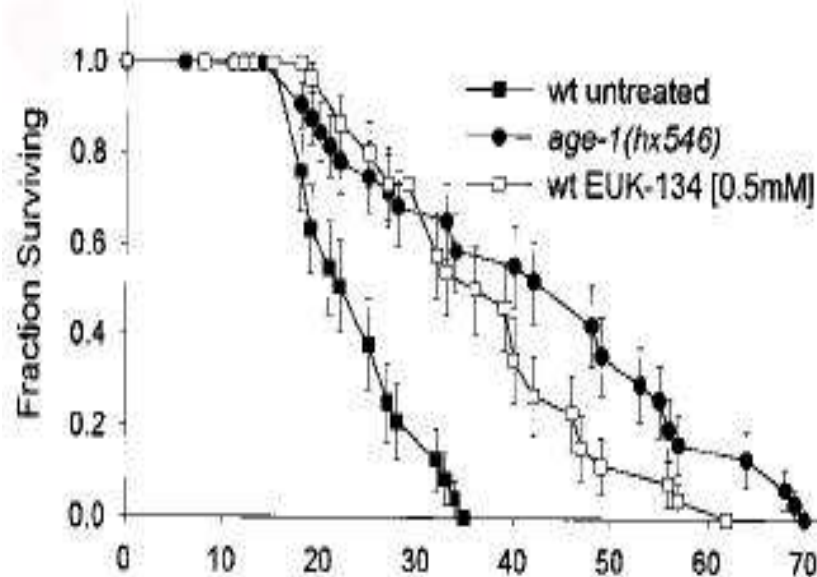


CAT

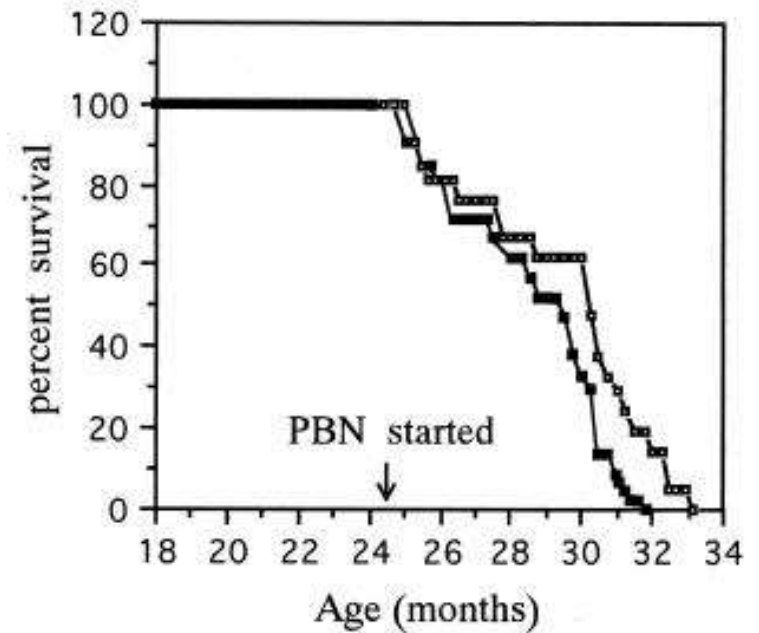


SOD

Increased animal lifespan by SOD/CAT mimetic (模拟物)



C. elegans



mice

Aging theories:

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- JNK signaling pathway

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- oxidative damage from reactive oxygen species (O_2^-)

4. Telomere (端粒) Theory

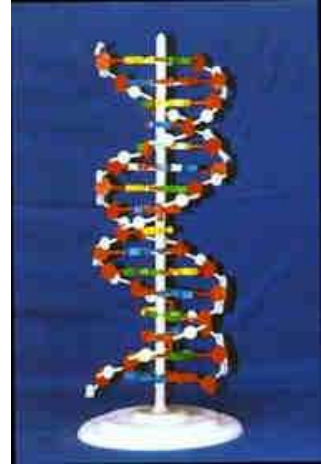
The Double Helix



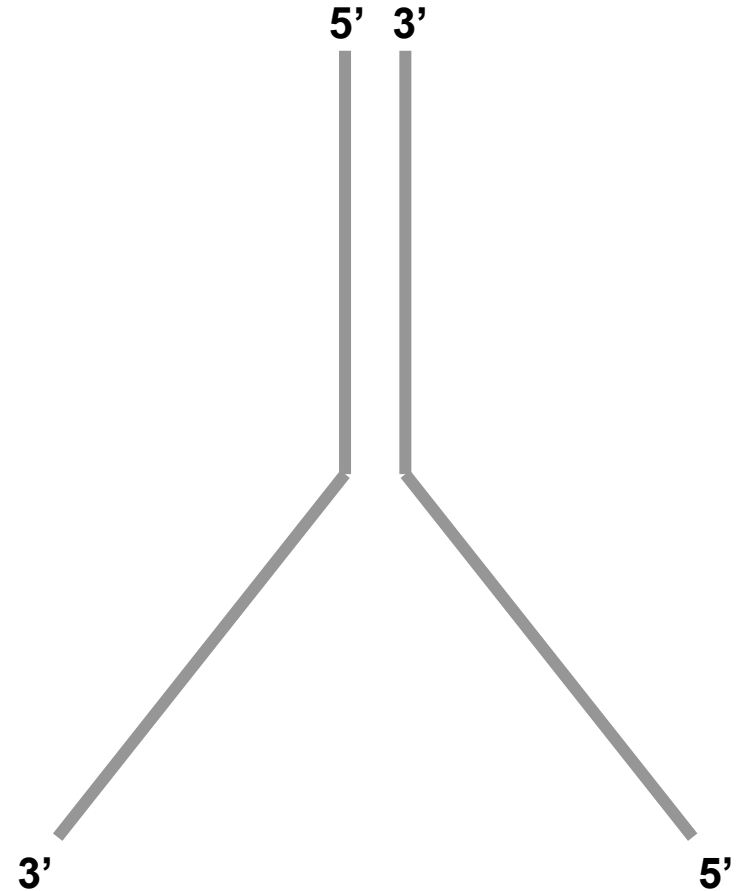
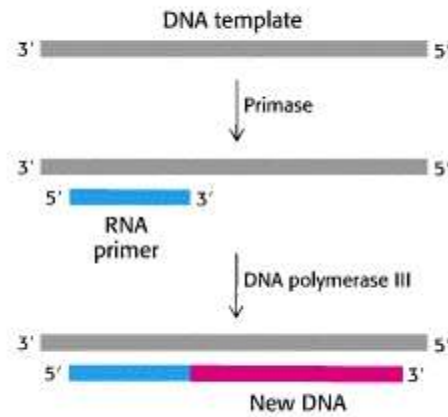
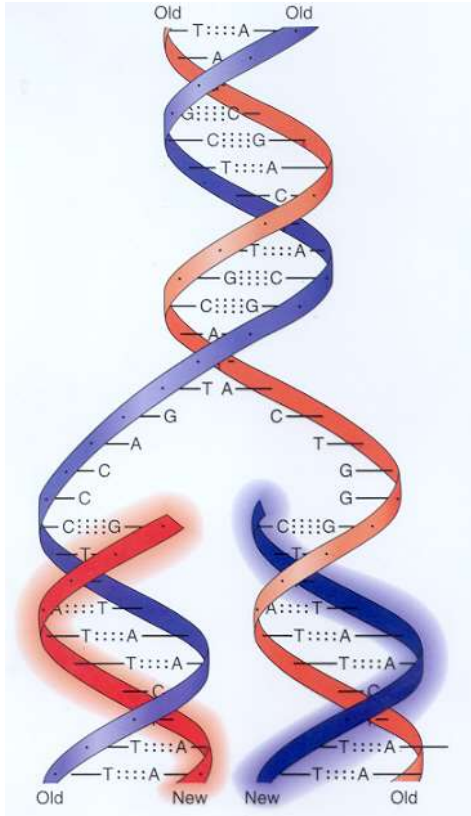
James Watson
1928-



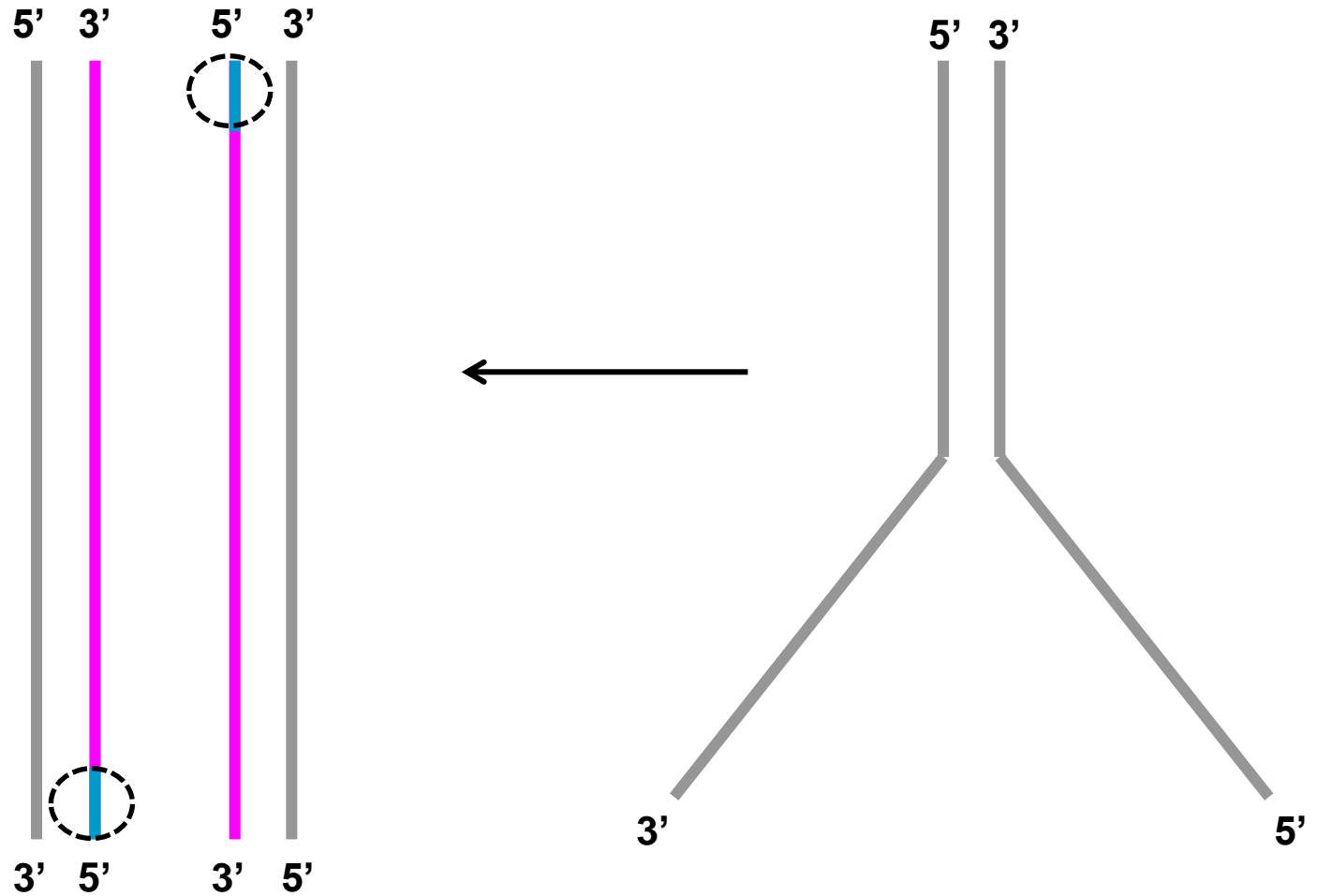
Francis Crick
1916 - 2004



DNA replication



DNA replication



The ends of chromosome shorten after each cell division?



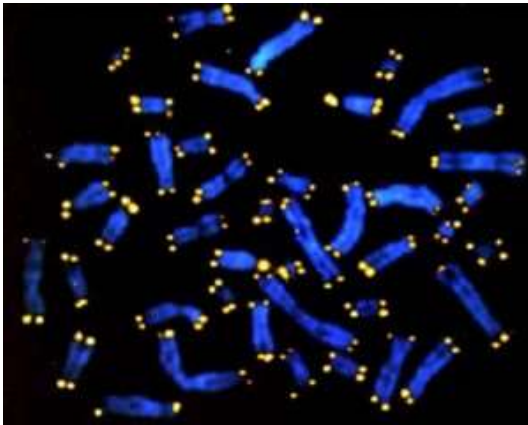
The Nobel Prize in Physiology or Medicine 2009

染色体

"for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase"

端粒

端粒酶



Elizabeth Blackburn

1978
telomere



Carol Greider

1985
Telomerase
(RNA)

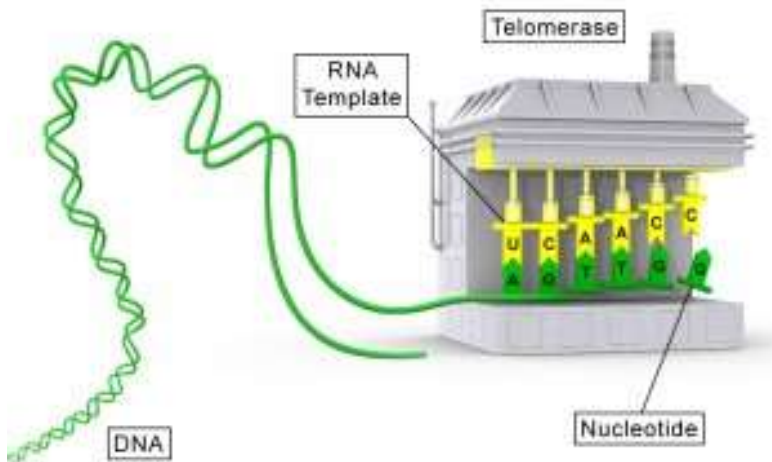


Jack Szostak

1982
artificial
chromosome



The Nobel Prize in Physiology or Medicine 2009



Elizabeth Blackburn

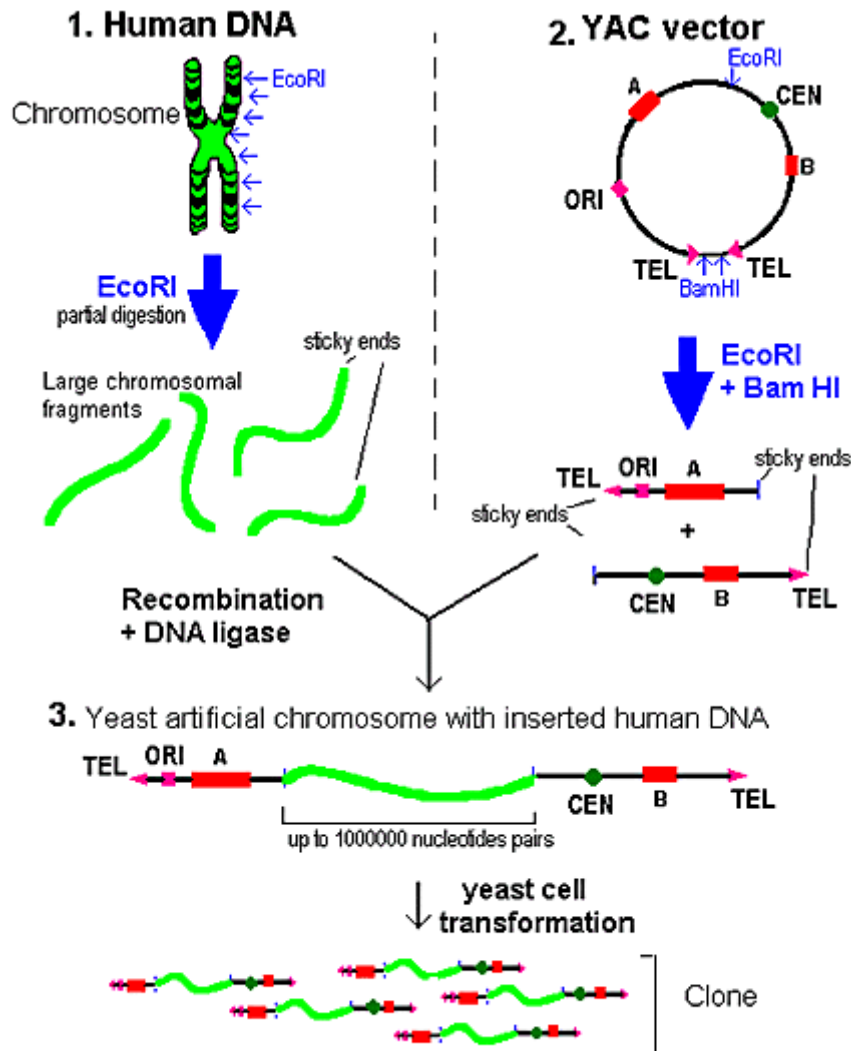
**1978
telomere**



**1985
Telomerase
(RNA)**



The Nobel Prize in Physiology or Medicine 2009



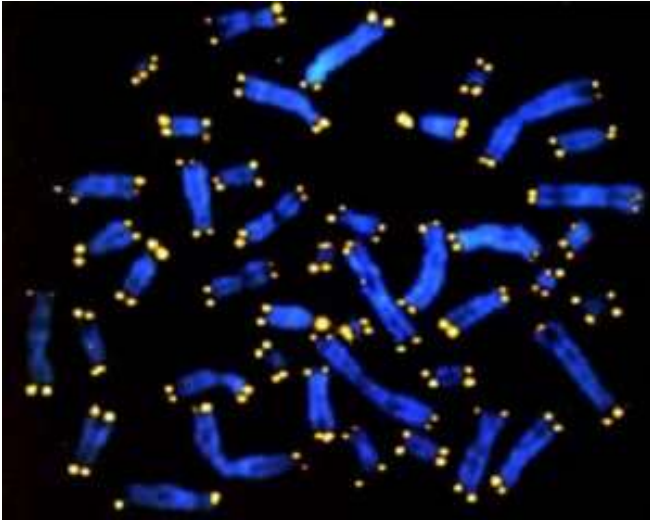
Jack Szostak

1982

**artificial
chromosome**

Cloning into a Yeast Artificial Chromosome (YAC)

Maintain of chromosome ends by **telomere**



Telomere:

- Composed of 6-8 base-pair-long repeats
human: **TTAGGG** repeat
- Length shortens with age
at birth: 11 kb
old age: 4 kb

Shorter telomeres: associated with diseases and aging

Rate of telomere shortening can be affected by:

genetics

telomerase activity

lifestyle - diet and activities

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4. Telomere Theory

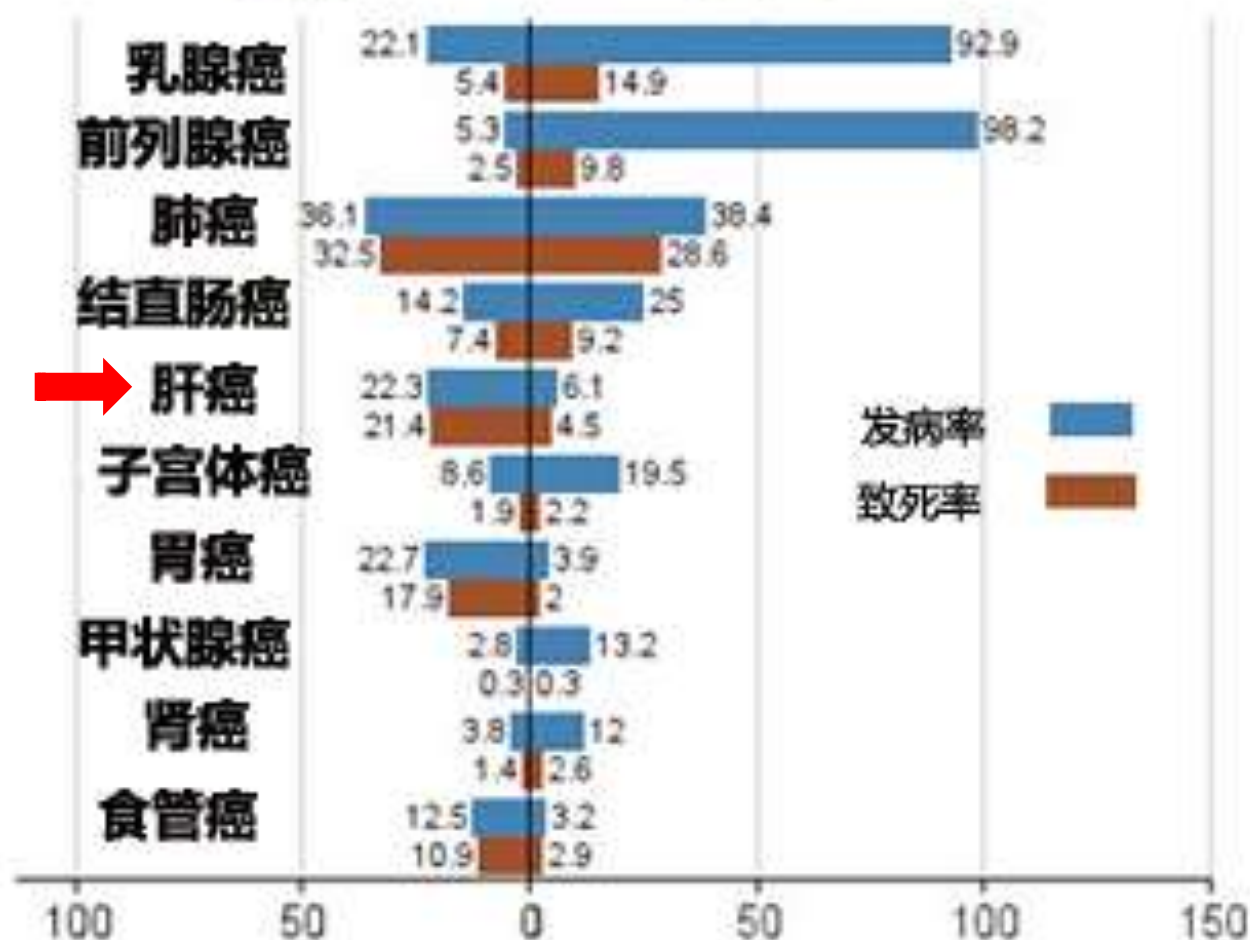
5. Accumulated mutation

- Mutations escape from proof reading and accumulate in somatic cells

ATCGTAG → ATCGTAG → ATCTTAG → ATCTGAG → ATCTGAG
TAGCATC → TAGAATC → TAGAATC → TAGAATC → TAGACTC

中国

美国



单位：/10万人（年龄标化率）

数据来源：国际癌症研究机构2012Globocan数据库

SHARE

RESEARCH ARTICLE | CANCER



Aristolochic acids and their derivatives are widely implicated in liver cancers in Taiwan and throughout Asia

Alvin W. T. Ng^{1,2,3,*}, Song Ling Poon^{4,*}, Mi Ni Huang^{1,2}, Jing Quan Lim^{4,5}, Arnoud Boot^{1,2}, Willie Yu^{1,2}, Yuka Suzuki^{1,2}, Sar...

+ See all authors and affiliations

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DOI: 10.1126/scitranslmed.aaan6446



Peer Reviewed
← see details

Science
Translational
Medicine

18 OCTOBER 2017



AAAS

马兜铃酸及其衍生物与台湾和亚洲的肝癌相关!

实验: 1400多例肝癌标本 - 是否存在马兜铃酸诱导的基因突变

结果: 亚洲人群的肝癌和马兜铃酸产生的突变高度相关

台湾 - 78%

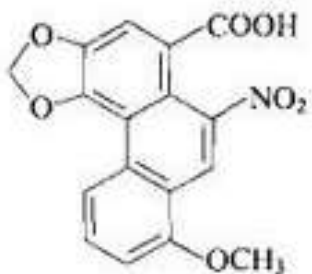
大陆 - 47%

越南 - 19%

北美 - 4.8%

欧洲 - 1.7%

马兜铃酸 (Aristolochic acid, AA)



- 1964，中国学者吴寒松报告两例“极型肾衰竭”病例 - 关木通煎剂。
- 1990，匈牙利，减肥女性出现肾衰竭 - 减肥药中的“广防己”。
- 1999，中国，龙胆泻肝丸，仅一家医院就有超过 100 名尿毒症患者。

马兜铃酸：导致尿毒症、肾癌、膀胱癌、尿道上皮癌等。

- 2001，世界卫生组织中提出对马兜铃酸药物的药物警报。
- 2002，美国 FDA 下令禁止使用一切含有马兜铃酸的草药。
- 2003，香港、台湾宣布停止进口及销售含有马兜铃酸的中草药材。
- 2008，国际癌症研究机构将马兜铃酸列为 1 类致癌物。

SHARE

RESEARCH ARTICLE CANCER



Genome-Wide Mutational Signatures of Aristolochic Acid and Its Application as a Screening Tool

马兜铃酸

Song Ling Poon^{1,2,*}, See-Tong Pang^{3,4,†}, John R. McPherson^{2,*}, Willie Yu^{1,2,4}, Kie Kyon Huang^{2,5}, ...
 * See all authors and affiliations

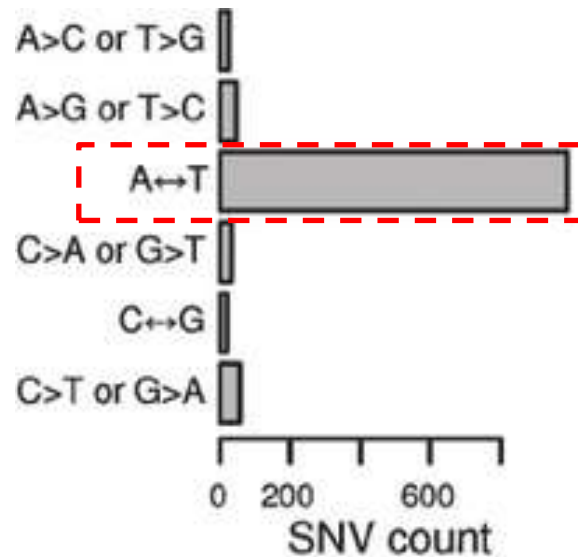
Science Translational Medicine 07 Aug 2013;
 Vol. 5, Issue 197, pp. 197ra101
 DOI: 10.1126/scitranslmed.3006086

AC/TAG

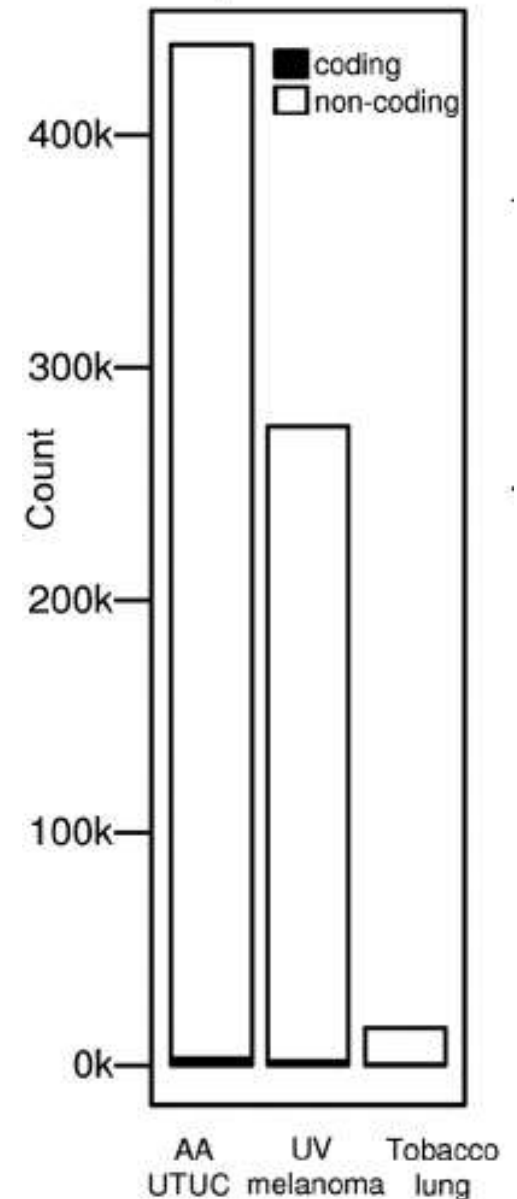


T

AA mutational signatures



Whole-genome sequencing all point mutations



含有马兜铃酸的中成药：

喘息灵胶囊，肺安片，复方蛇胆川贝散，鸡鸣丸，鸡苏丸，七十味松石丸，十三味疏肝胶囊，胃福颗粒，消咳平喘口服液，新碧桃片，香藤胶囊，杜仲壮骨胶囊，杜仲壮骨丸，风湿宁药酒，复方风湿药酒，复方拳参片，祛风除湿药酒，少林正骨精，伤湿镇痛膏，神农药酒，金朱止泻片，保胃胶囊，复方胃痛胶囊，九龙解毒胶囊，三蛇药酒，龙胆泻肝丸，耳聋丸，八正丸，纯阳正气丸，大黄清胃丸，当归四逆丸，当归四逆汤，导赤丸，甘露消毒丸，排石颗粒，跌打丸，妇科分清丸，冠心苏合丸，苏合丸，辛荑丸，十香返生丸，济生橘核丸，止咳化痰丸，八正合剂，小儿金丹片，分清五淋丸，安阳精制膏，儿童清肺丸，九味羌活丸，川节茶调丸，小儿咳喘颗粒，小青龙合剂，猴枣散。

Aging

Cloning

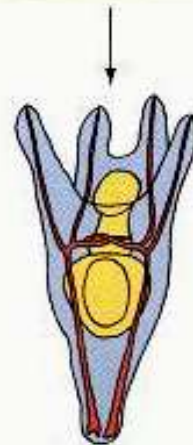


Hans Driesch
1892

Early embryonic cells are **totipotent**

早期胚胎细胞具有**全能性**

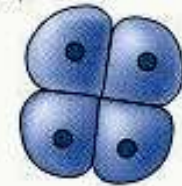
(A) Fertilization envelope



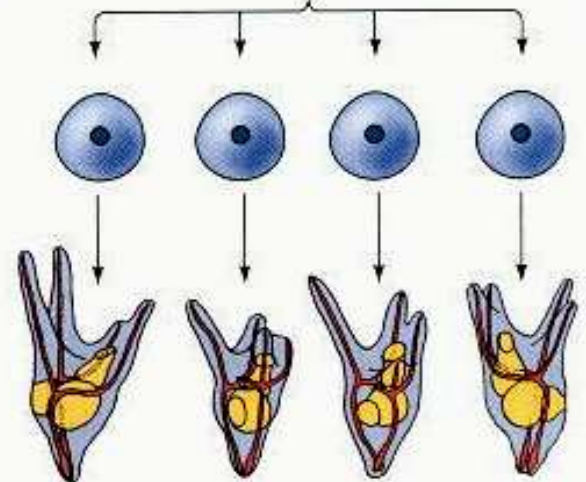
Normal pluteus
larva

(B)

Remove
fertilization
envelope



Separate
into 4 cells

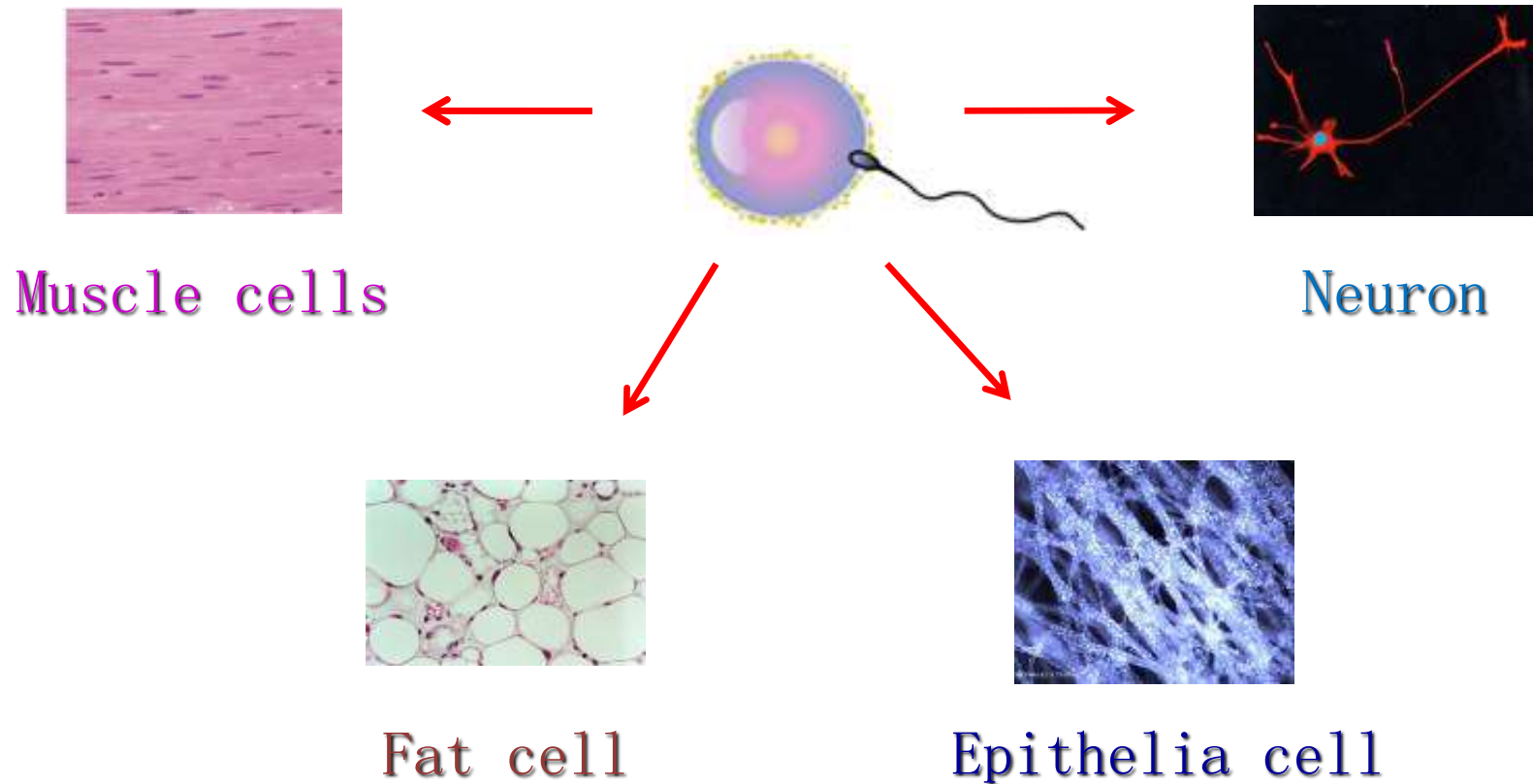


Plutei developed from
single cells of 4-cell embryo

成熟、已分化的细胞呢？

Do fully differentiated cells have totipotency ?

完全分化的细胞是否还有全能性？





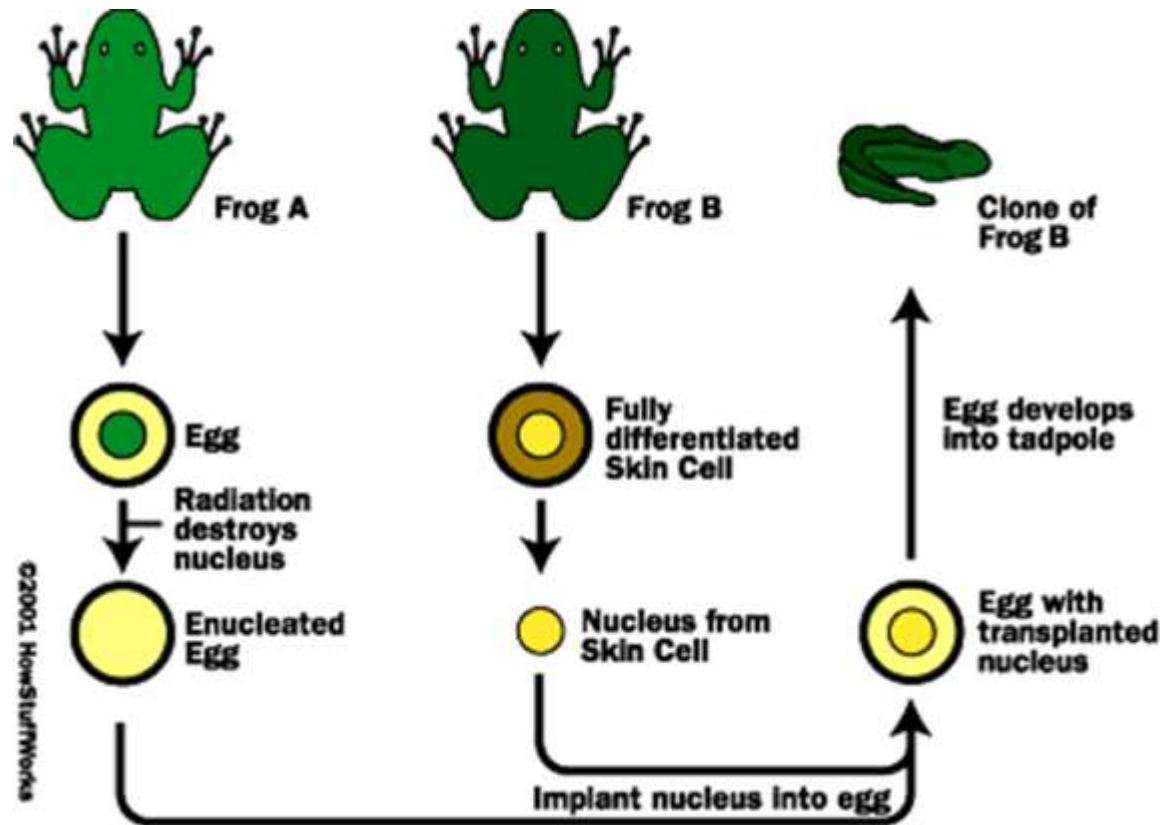


The Nobel Prize in Physiology or Medicine 2012

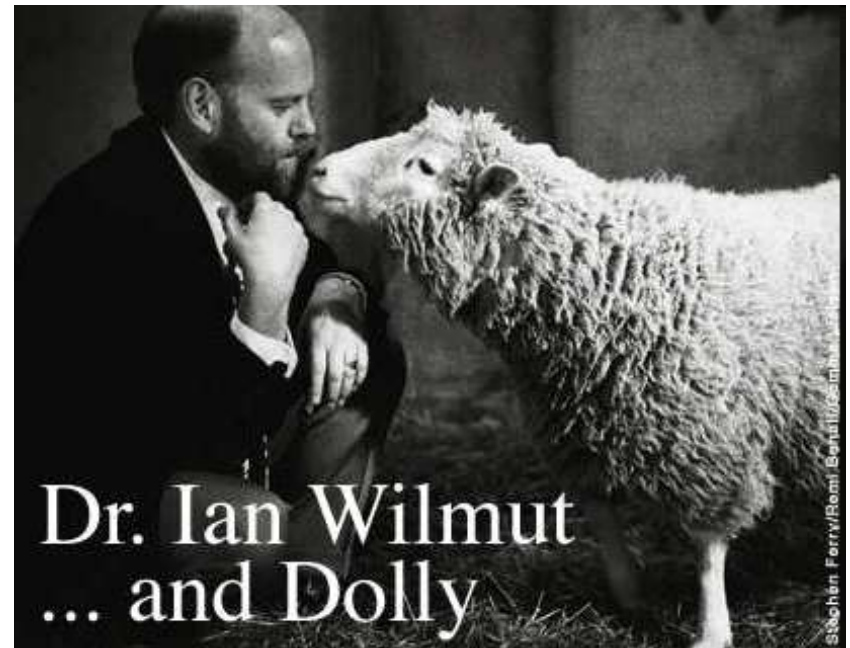
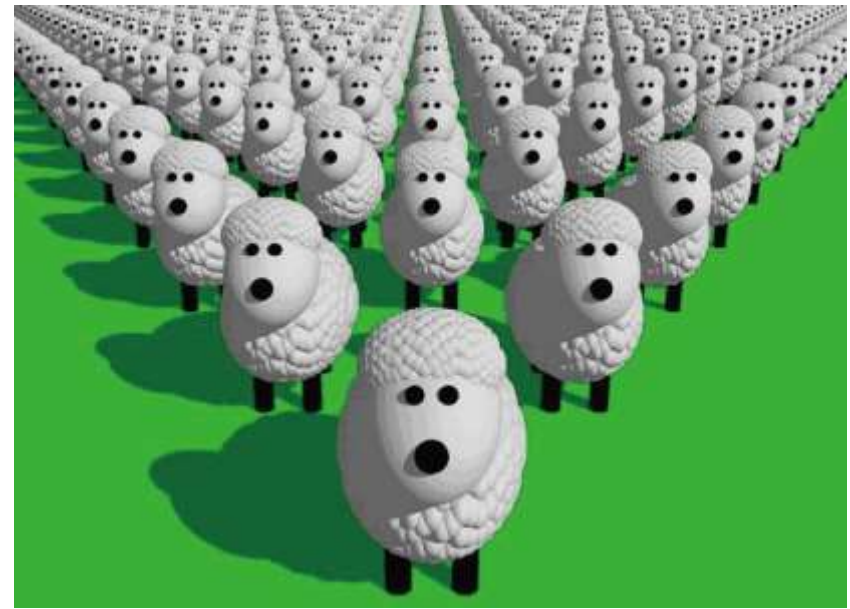
"for the discovery that mature cells can be reprogrammed to become pluripotent"



John B. Gurdon
1933 –



How about mammal?



1996

Cloning - Future application



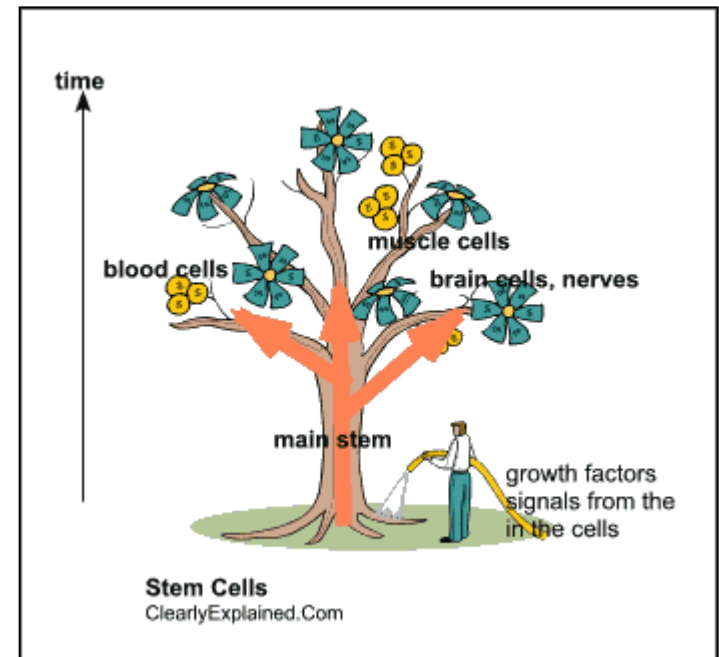
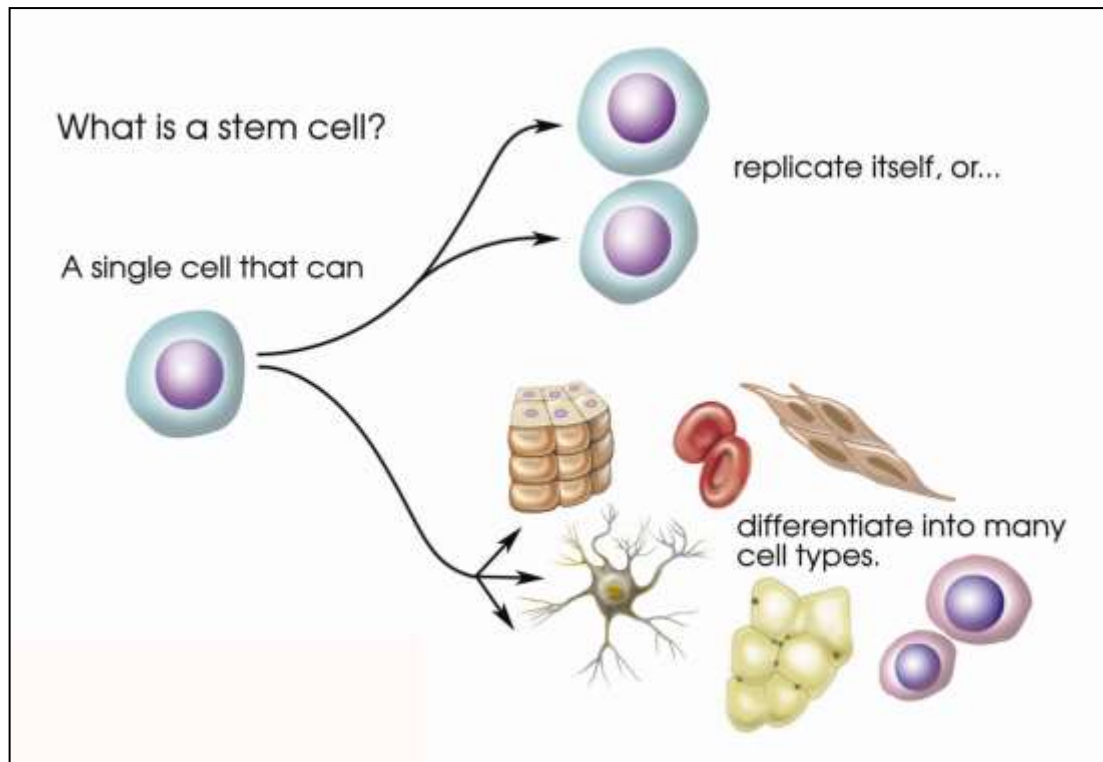
Aging

Cloning

Stem cell

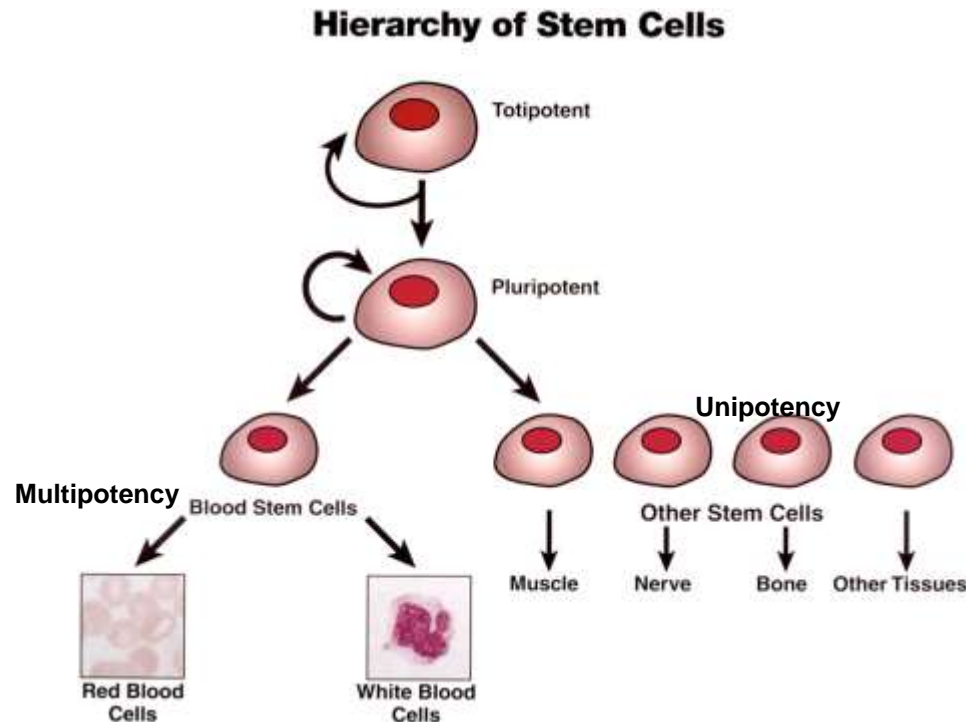
Stem cells:

- Ability to **renew** through mitotic cell division
- Ability to **differentiate** into specialized cells



Potency of stem cells:

1. **Totipotency** 全能: produce all the differentiated cells in an organism.
2. **Pluripotency** 多能: differentiate into any of the three germ layers
- endoderm, mesoderm, or ectoderm.
3. **Multipotency** 复能: give rise to multiple, but limited cell lineages.
4. **Unipotency** 单能: differentiate into only one type of cell.



Origin of stem cells

1. Embryonic stem cells (ESc)

From the inner cell mass of blastocysts

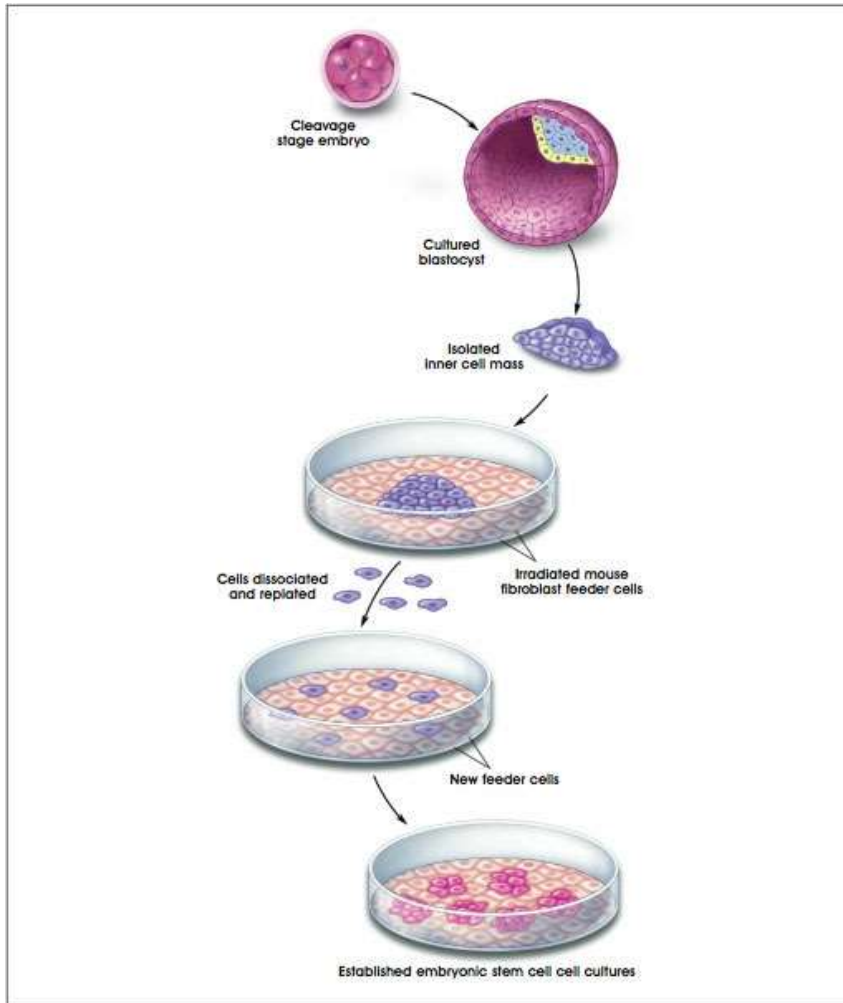
2. Adult stem cells

From adult tissues

3. Induced pluripotent stem cells (iPSc)

From adult tissue

Embryonic stem cells (ESc): from the inner cell mass of blastocysts



Martin Evans

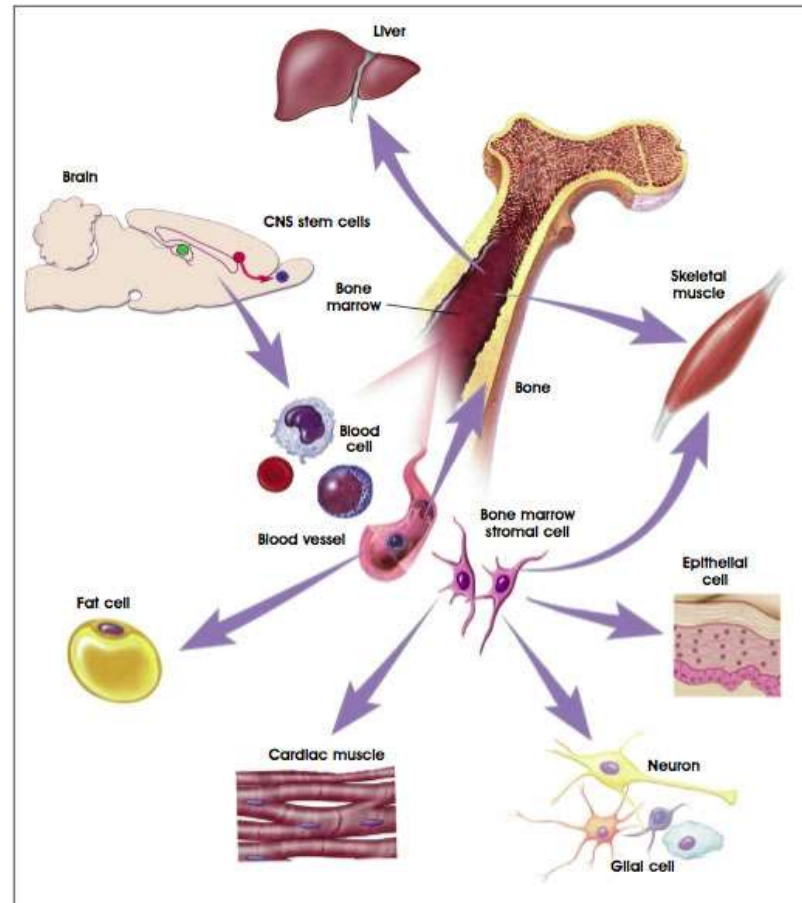


**The Nobel Prize in
Physiology or Medicine 2009**

1981, Martin Evans & Matthew Kaufman

Adult stem cells: From adult tissues

- Maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues
- Repair damaged tissues

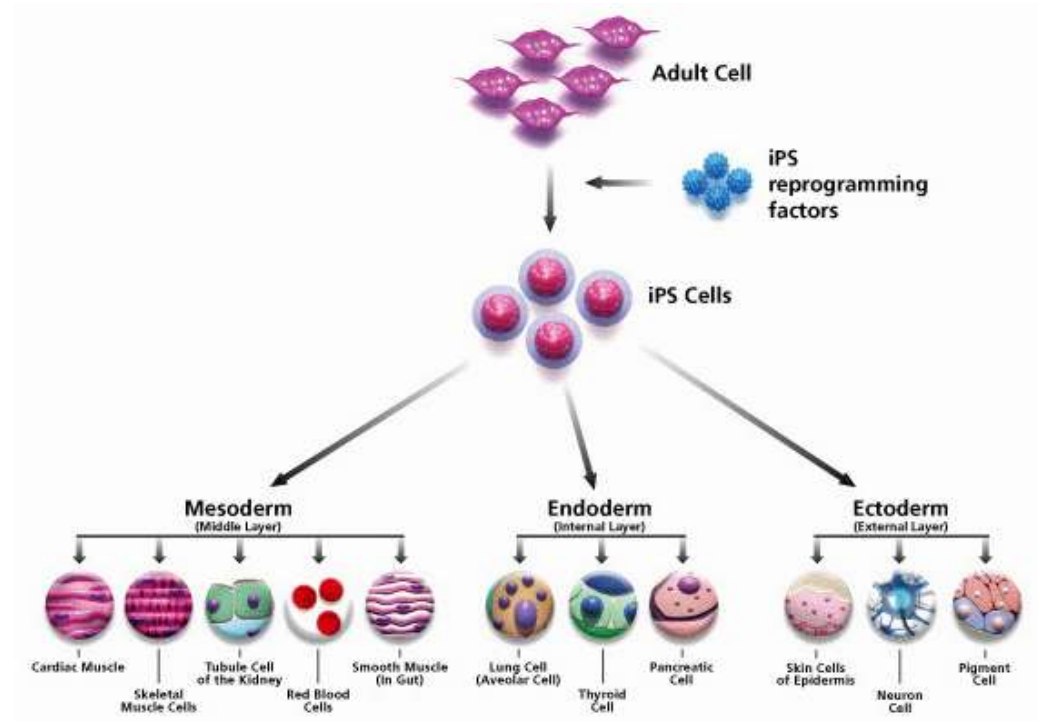


Induced pluripotent stem cells (iPSc): From adult tissue

- Induced by forced expression of transcription factors
- Equivalent to embryonic stem cells



Shinya Yamanaka



The Nobel Prize in Physiology or Medicine 2012

Stem cells → Organ cloning

