HKU Study on Stem Cell and Aging: Revealing Anti-aging Genetic Mechanism
港大幹細胞及老化研究 發現抗衰老啟動機制

Dr Zhou Zhongjun
Associate Professor
Department of Biochemistry
The University of Hong Kong Li Ka Shing Faculty of Medicine

香港大學李嘉誠醫學院
生物化學系
副教授
周中軍博士

Dr Liu Baohua
Research Assistant Professor
Department of Biochemistry
The University of Hong Kong Li Ka Shing Faculty of Medicine

香港大學李嘉誠醫學院
生物化學系
助理教授（研究）
劉寶華博士

Hutchinson-Gilford Progeria Syndrome (HGPS)
早老症

8-year-old Mateo and 10-year-old Milagros in 2010 --- From ***Progeria Research Foundation***

Rare genetic disease of early onset severe premature aging
罕見兒童早老症

About HGPS
關於早老症

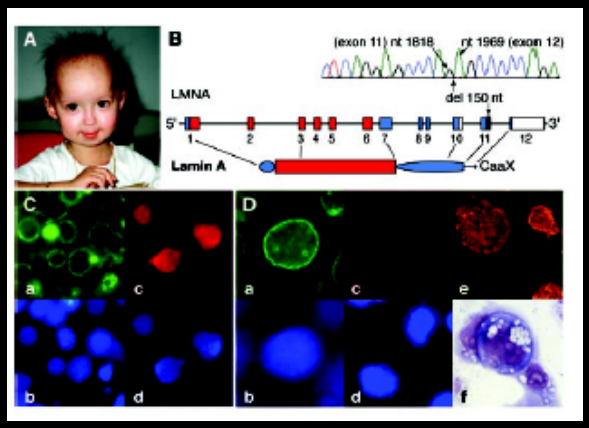
- About 5-10 times faster than normal aging rate
  衰老速度為正常人的5-10倍
- Can live 7-20 years, average life span 13 years
  可存活至7-20多歲，平均存活時間13年
- 90% die of aging diseases such as heart problems
  90%病人死於衰老病如心臟疾病

Physical and Clinical Features
臨床特徵

- Dwarfism and retarded growth 身材矮小
- Wrinkled/aged-looking skin 皮膚老化
- Pinched nose 鷹勾鼻
- Hair loss 脫髮
- Loss of body fat 皮下脂肪減少
- Delayed tooth formation 較晚長牙
- Stiff joints 關節硬化
- Hip dislocation 髖關節脫臼
- Buildup of plaques in the arteries (atherosclerosis) 動脈硬化
- Heart disease or stroke 心血管疾病
  中風 (心肌梗塞或鬱血性心衰竭)

4-year-old Cameron
我四歲了！
--- From *Progeria Research Foundation*

HGPS: caused by heterozygous mutation in Lamin A
核纖層蛋白 A 變異導致早老症



Eriksson, *et al.* Nature (2003)

Cause of HGPS identified in 2003 by Francis Collins who is NIH director
2003年，美國國立衛生研究院 Francis Collins 實驗室發現導致早老症的成因

From Lamin A mutation to HGPS
由核纖層蛋白 A 變異至早老的機制

Mutation in Lamin A
核纖層蛋白 A 變異

↓

Truncated pre-Lamin A (Progerin)
截短的核纖層蛋白 A（早老素）

↓

HGPS

What is Lamin A?

A nuclear matrix protein encoded by *LMNA* gene。

核纖層蛋白 A 是細胞核內一種基質蛋白質，是由核纖層蛋白 A 基因編碼而來。

Three Unsolved Questions about HGPS

有關早老症的三大疑問

1. **Why and how does the malfunctioned Lamin A cause premature aging?**
   為何核纖層蛋白 A 突變會導致早老症 **?**

2. **Does stem cell contribute to aging ?**
   幹細胞在早老症中對快速衰老有何作用**?**

3. **Is there any cure for HGPS ?**
   早老症有救嗎？

Previous Studies on Accelerated Aging by HKU

港大早老症研究

Question 1

1. Why and how does the malfunctioned Lamin A cause premature aging?

為何核纖層蛋白 A 突變會導致早老症？

Convergent mechanism between HGPS and normal aging
與正常衰老的機理類似

Approach and Methodology
研究方法

- **Mouse Model + Human Study (human cells from HGPS patients)**
  利用老鼠模型及病人細胞進行研究

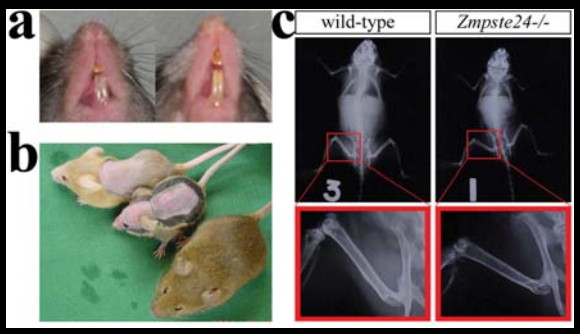
Mouse Model for HGPS
早老症動物模型

Genetically manipulated mice with unprocessed prelamin A
Prelamin A is similar to Progerin
Recapitulate accelerated aging symptoms of HGPS

植入核纖層蛋白A前體到遺傳修飾小鼠
核纖層蛋白A前體與早老素類似
呈現早老症徵狀

小鼠表現出與早老症病人相同的快速衰老徵狀

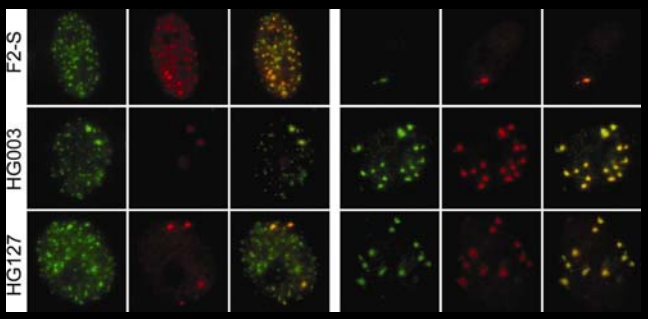
Mouse Models showed they have similar accelerated aging symptoms of HGPS patients



Pendas, Zhou, *et al* *Nature Genetics* (2002)

Progerin (Mutated Lamin A) → leading to defective DNA repair → increase genomic instability → accelerated aging
早老素造成DNA 損傷，未能修復缺陷→導致基因組不穩定→加速老化

10 minutes after DNA damage 12 hours after DNA damage

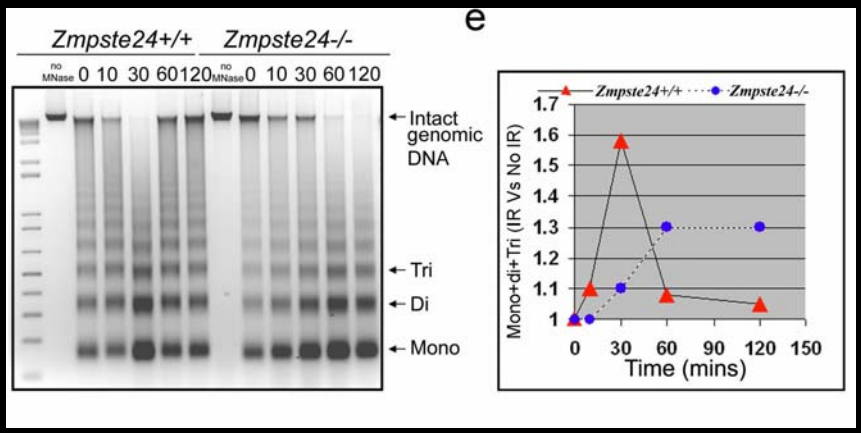


Liu, *et al.* *Nature Medicine*, 2005

Why does progerin affect DNA repair?

Progerin leads to defective chromatin remodeling which is necessary for DNA repair

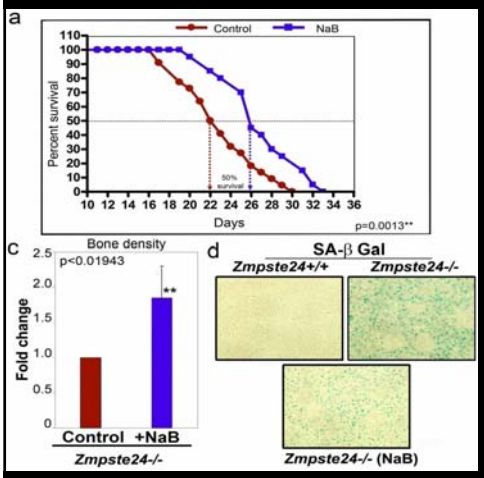
早老素導致染色質重構缺陷，繼而引致DNA損傷，修復不能有效進行



Liu, *et al. Aging Cell 2012*

Rescue of accelerated aging by small chemical restoring chromatin remodeling and DNA repair

重組染色質結構及恢復DNA損傷修復能力，可顯著改善早老症狀並延長壽命



NaB-treated Zmpste24-/- Zmpste24-/- WT

Krishnan, *et al. Proc Natl Aca Sci USA*, 2011

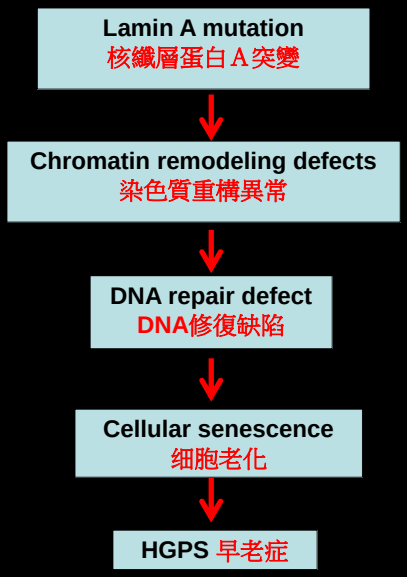
Summary of Previous Studies
前期研究總結

Answer to Question 1:

Malfunctioned Lamin A causes premature aging

解答疑問一：

核纖層蛋白Ａ突變會導致早老症



Recent Advance in the Accelerated Aging Study by HKU

港大早老症研究新進展

Question 2 & 3

2. Does stem cell contribute to aging？
幹細胞在早老症中對快速衰老有何作用**?**

3. Is there any cure for HGPS？
早老症有救嗎？

Our latest discovery:
link between SIRT1 and HGPS
最新研究發現：
長壽基因**SIRT1**與早老症的關聯

- **Adult stem cells decline prior to accelerated aging in mouse model of HGPS**
  成體幹細胞在小鼠模型出現早老之前迅速減少

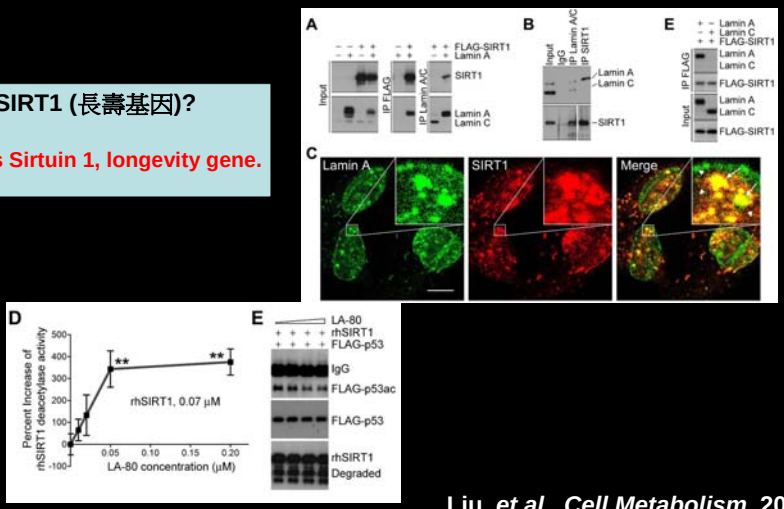
- **Activates SIRT1 longevity gene to rescuing adult stem cells, and thus ameliorates premature aging and extends lifespan**
  刺激長壽基因**SIRT1**以促進成體幹細胞自我複製，延緩出現早老表徵，延長小鼠壽命

Liu, *et al.* Cell Metabolism, 2012

1. Lamin A interacts with and activates SIRT1
Binding to Lamin A is critical for SIRT1 activity
核纖層蛋白 A 結合並刺激長壽基因SIRT1
與核纖層蛋白 A 結合能有效提升長壽基因SIRT1的活性

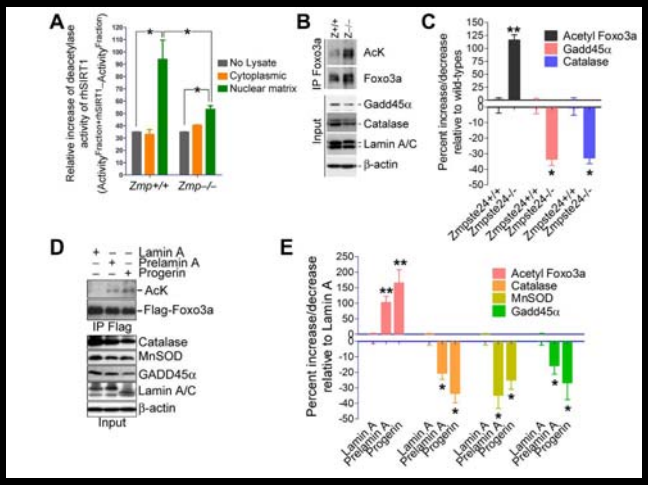
What is SIRT1 (長壽基因)?

Known as Sirtuin 1, longevity gene.



Liu, *et al.* *Cell Metabolism*, 2012

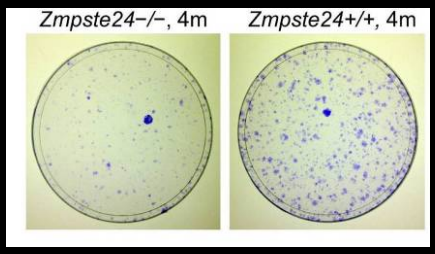
2. Reduced SIRT1 activity in HGPS
with the existence of Progerin
早老素導致長壽基因SIRT1的活性下降

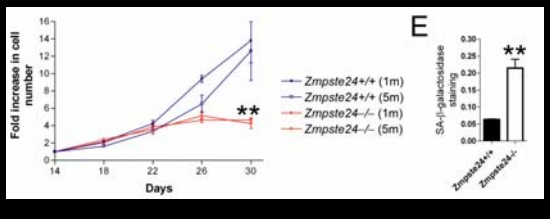


Liu, *et al.* Cell Metabolism, 2012

3. Decreased SIRT1 activity causes stem cell to decline in HGPS mouse model

早老小鼠的長壽基因SIRT1活性下降
導致幹細胞數量與功能降低





Liu, *et al.* Cell Metabolism, 2012

Another focus of the study:
How does Resveratrol activate SIRT1?

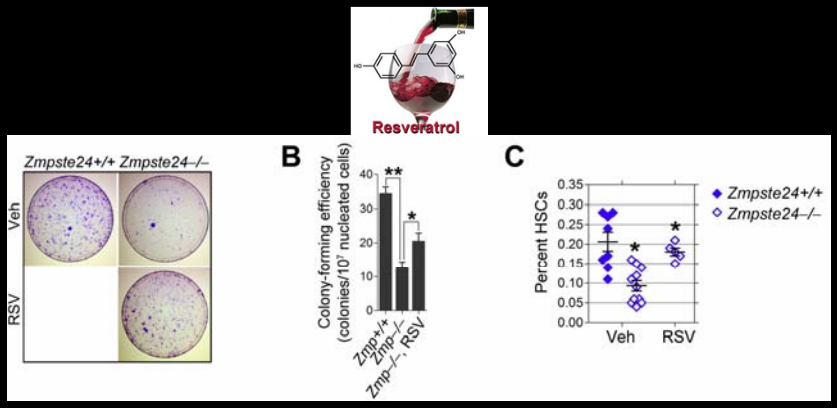
白藜蘆醇如何刺激長壽基因SIRT1？

- **Resveratrol is found in the skin of red grapes and in other fruits**
- 葡萄及其他水果皮含有白藜蘆醇

- **There is a saying that the Resveratrol is effective in anti-aging, is it true?**
- 白藜蘆醇被指可延長壽命，是否真確？

4. Resveratrol enhances binding of SIRT1 to Lamin A, increases SIRT1 activity to protect stem cells

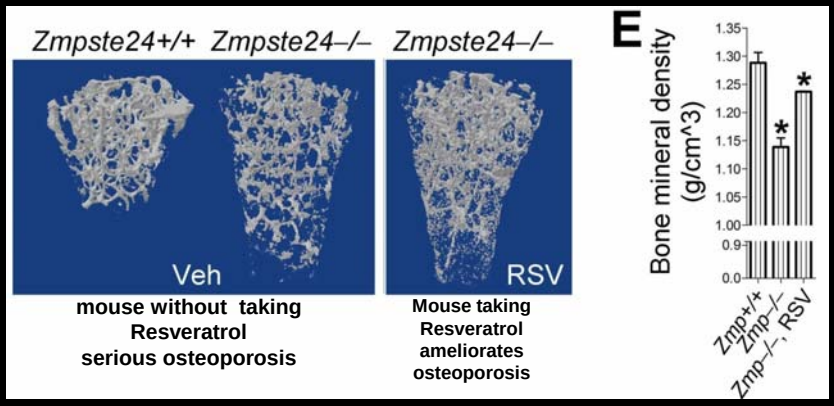
白藜蘆醇通過刺激核纖層蛋白A與長壽基因SIRT1的結合，增強SIRT1的活性，促進幹細胞自我更新功能



Liu, *et al.* Cell Metabolism, 2012

5. Resveratrol activates the SIRT1 anti-aging mechanism and ameliorates premature aging such as osteoporosis in HGPS mouse model

白藜蘆醇啟動SIRT1抗衰老機制
從而改善衰老症狀如骨質疏鬆



mouse without taking Resveratrol serious osteoporosis

Mouse taking Resveratrol ameliorates osteoporosis

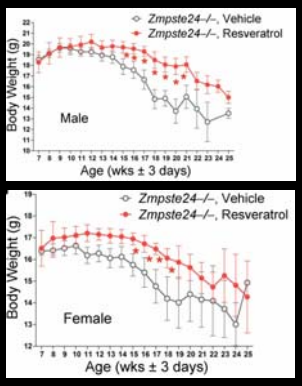
未使用白藜蘆醇
骨質疏鬆情況嚴重

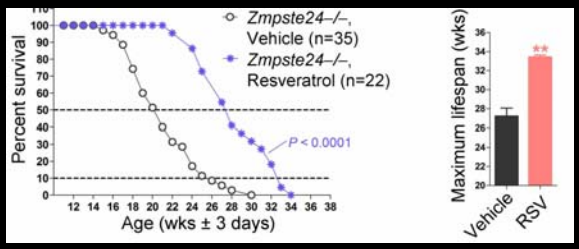
使用白藜蘆醇後
骨質疏鬆情況得以改善

Liu, *et al.* Cell Metabolism, 2012

Resveratrol increases bodyweight and extends lifespan in HGPS mouse model

白藜蘆醇增加早老症小鼠體重，延長壽命





有服食白藜蘆醇的早老症小鼠較對照組小鼠的體重為高，老化延遲，壽命延長

Liu, *et al.* Cell Metabolism, 2012

Recent Studies on Accelerated Aging

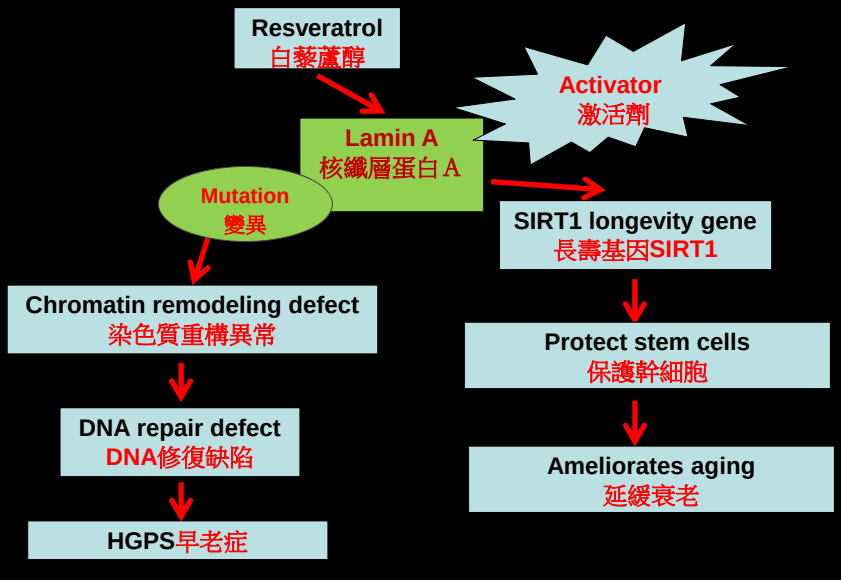
Answer to Question 2 & 3:

- **Stem cell contributes to aging**
- **There is novel therapeutic strategy for HGPS**

解答疑問二及三：

- 幹細胞在早老症中對快速衰老發揮作用
- 早老症有治療新方向

Studies through Year 2005 to 2012
2005至2012年的研究



CONCLUSIONS
結論

1. **Lamin A is an endogoneous activator of SIRT1**
   核纖層蛋白A是長壽基因SIRT1的內源啟動劑

2. **Lamin A mutation leads to decreased SIRT1 activity and early stem cells to decline which contributes to HGPS**
   核纖層蛋白A突變導致長壽基因SIRT1活性下降及幹細胞數目減少，繼而導致早老症

3. **Resveratrol activates SIRT1 through Lamin A, rescues early decline of stem cells, ameliorates premature aging symptoms and extends lifespan**
   白藜蘆醇通過 Lamin A刺激長壽基因SIRT1，促進幹細胞自我增生，延緩早老並延長壽命

Significance of our findings
此項研究發現的意義

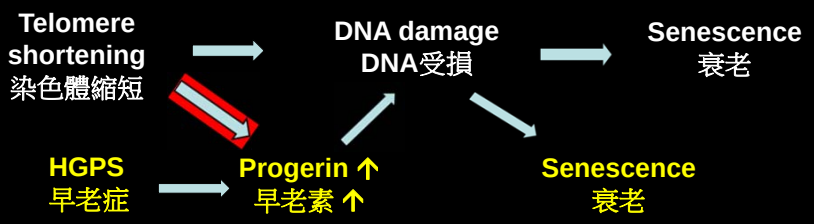
- **The first time to link HGPS to SIRT1 pathway**
  國際首次報導早老症與長壽基因SIRT1的關聯機制
- **Broaden our knowledge of Lamin A biological functions**
  發現Lamin A新的生物學功能
- **Reveal mechanism by which Resveratrol activates SIRT1**
  揭示白藜蘆醇刺激長壽基因SIRT1的分子機理
- **Help to understand normal aging processes**
  有助瞭解正常衰老的過程
- **Novel stem cell therapy targeting HGPS and aging-associated degenerative diseases**
  建立針對早老症及衰老相關疾病的新靶蛋白以及幹細胞治療新策略

The research findings have been published in the leading biological journal - *Cell Metabolism* on Dec 5, 2012 (HK Time)

此項突球性研究成果已於二零一二年十二月五日於國際權威生物學期刊 —《細胞代謝》上發表

Link between HGPS and normal aging?

早老症與正常衰老有關係嗎？



Progerin production increases as we are getting old

早老素存在於正常細胞中並在衰老過程中累積

Perspectives

展望

1. **People in HK is the most long-lived in the world and the cost for elderly healthcare is increasing. There is an urgent need for substantial government funding for basic research on aging to extend healthy span and to reduce the cost in healthcare.**

   香港人是世界上最長壽的一群，老年相關醫療支出持續攀升。呼籲政府對衰老基礎研究增加投入，從而延長香港人的健康壽命及降低相關醫療費用。

2. **Novel therapeutic strategies against aging-associated degenerative diseases including neurological, cardiovascular and skeletal disorders.**

   研究及建立新的治療及預防措施，以應對老年相關疾病（包括神經、心血管及骨骼疾病）

3. **Develop new drug mimicking Lamin A to target on SIRT1**

   開發類似Lamin A 的新型藥物，刺激長壽基因SIRT1

Research Team Members
研究團隊

Zhongjun Zhou (周中軍) , Baohua Liu (劉寶華) , Shrestha Ghosh, Xi Yang (楊熙) , Zimei Wang (王子梅)

Department of Biochemistry, The University of Hong Kong Li Ka Shing Faculty of Medicine
香港大學李嘉誠醫學院生物化學系

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