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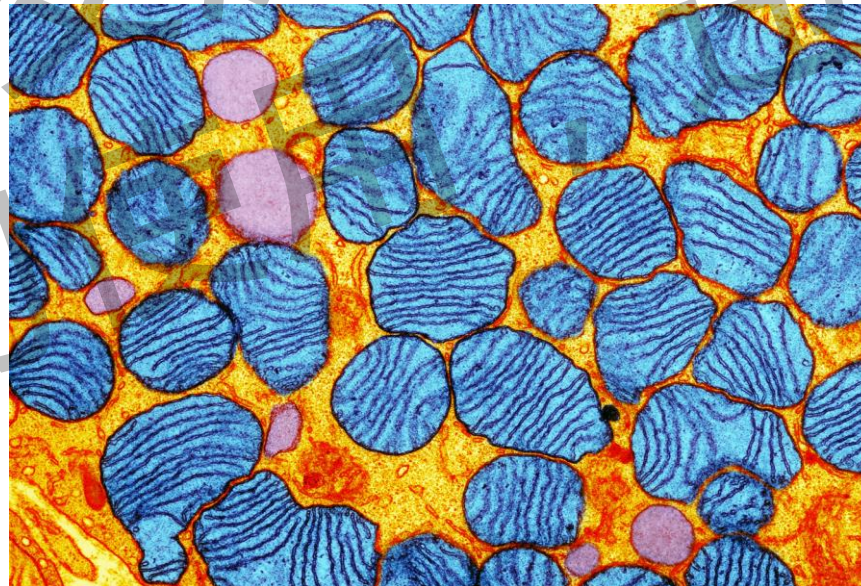
武汉 – 2018年11月30日

“MOTS-c 运动基因组SNP 是亚洲男性糖尿病发病的高危因素”

Pinchas Cohen, MD

Dean **USC** Leonard Davis

School of Gerontology

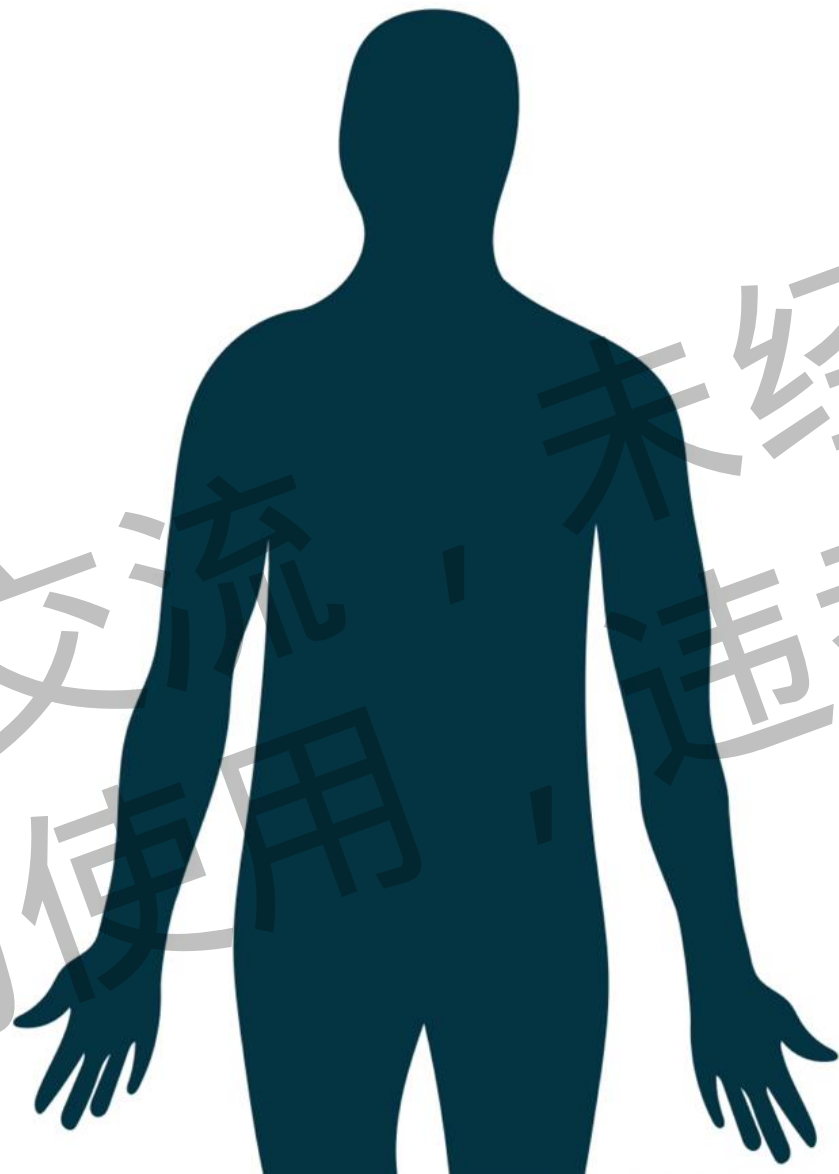


COI Disclosure

Pinchas Cohen, MD

Advisory Role/Stock Ownership - **CohBar Inc**

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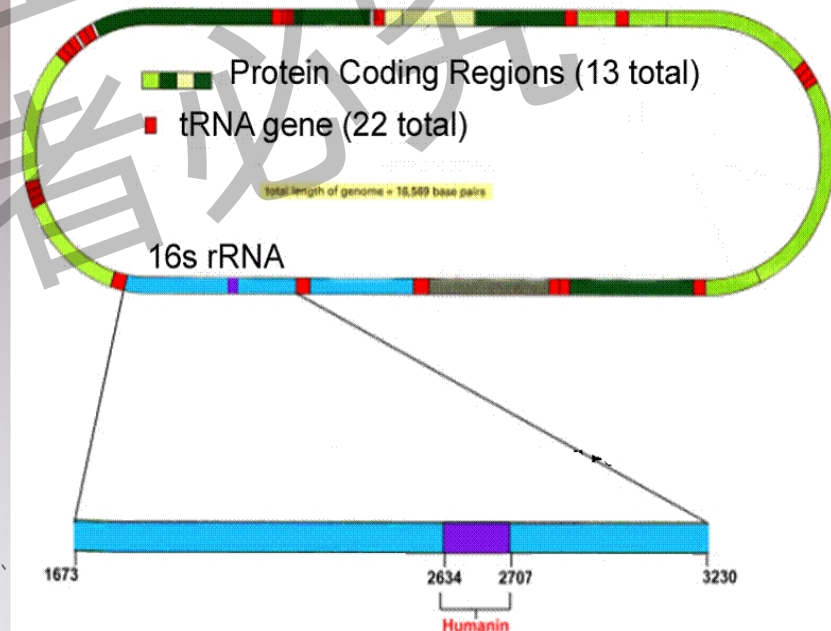
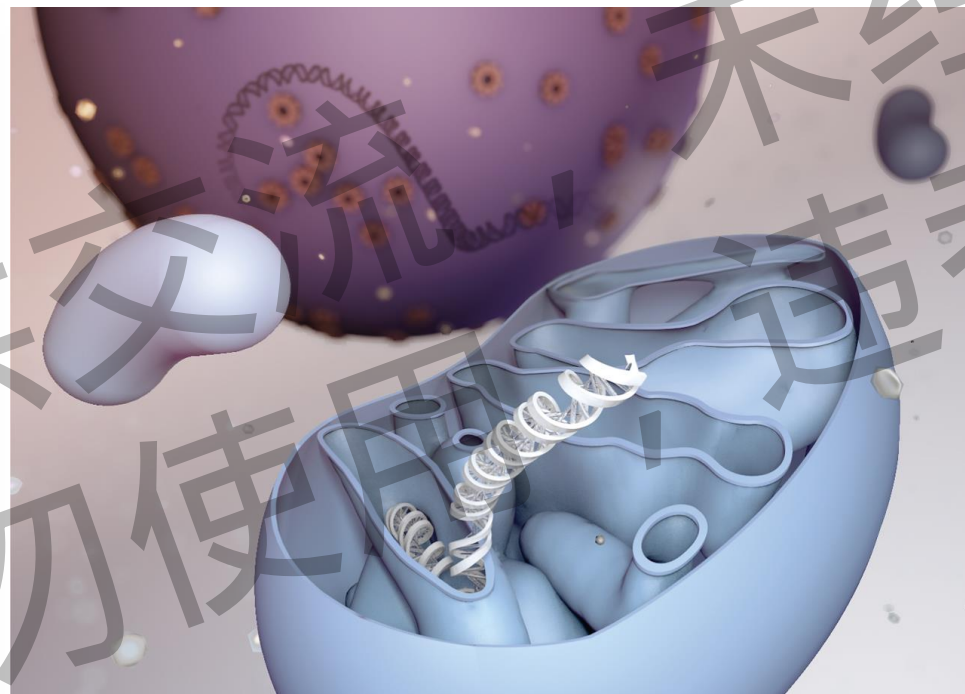
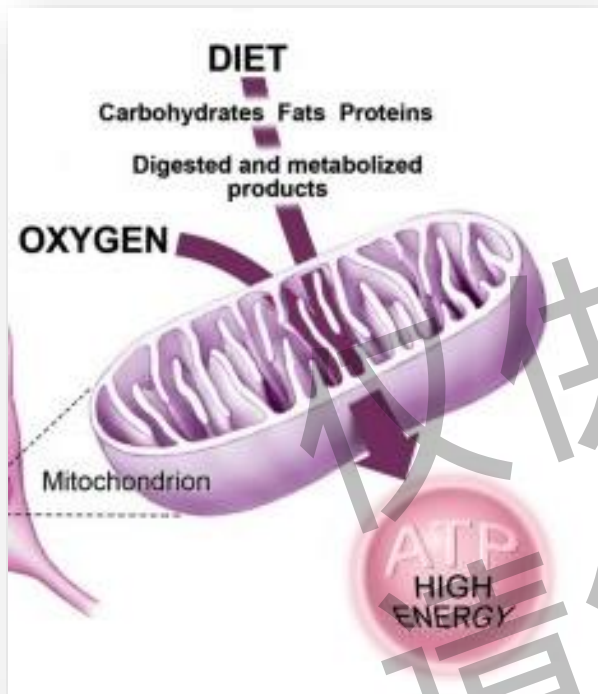


线粒体系统的生物学

- 线粒体多肽: 结构, 功能 & 信号通路
- 线粒体基因组学
- 线粒体转录组学
- 线粒体表观遗传学
- 线粒体多肽组学
- 线粒体人群基因组学
- MDP方法作为诊断及判断预后的工具
- MDP科学在新药物发现中的作用

基础的线粒体生物学

- 来源与共生细菌; **母系遗传**
- 线粒体功能**随年龄增加而减退**
- 参与寿命、阿尔茨海默氏症、**糖尿病**、**肿瘤**

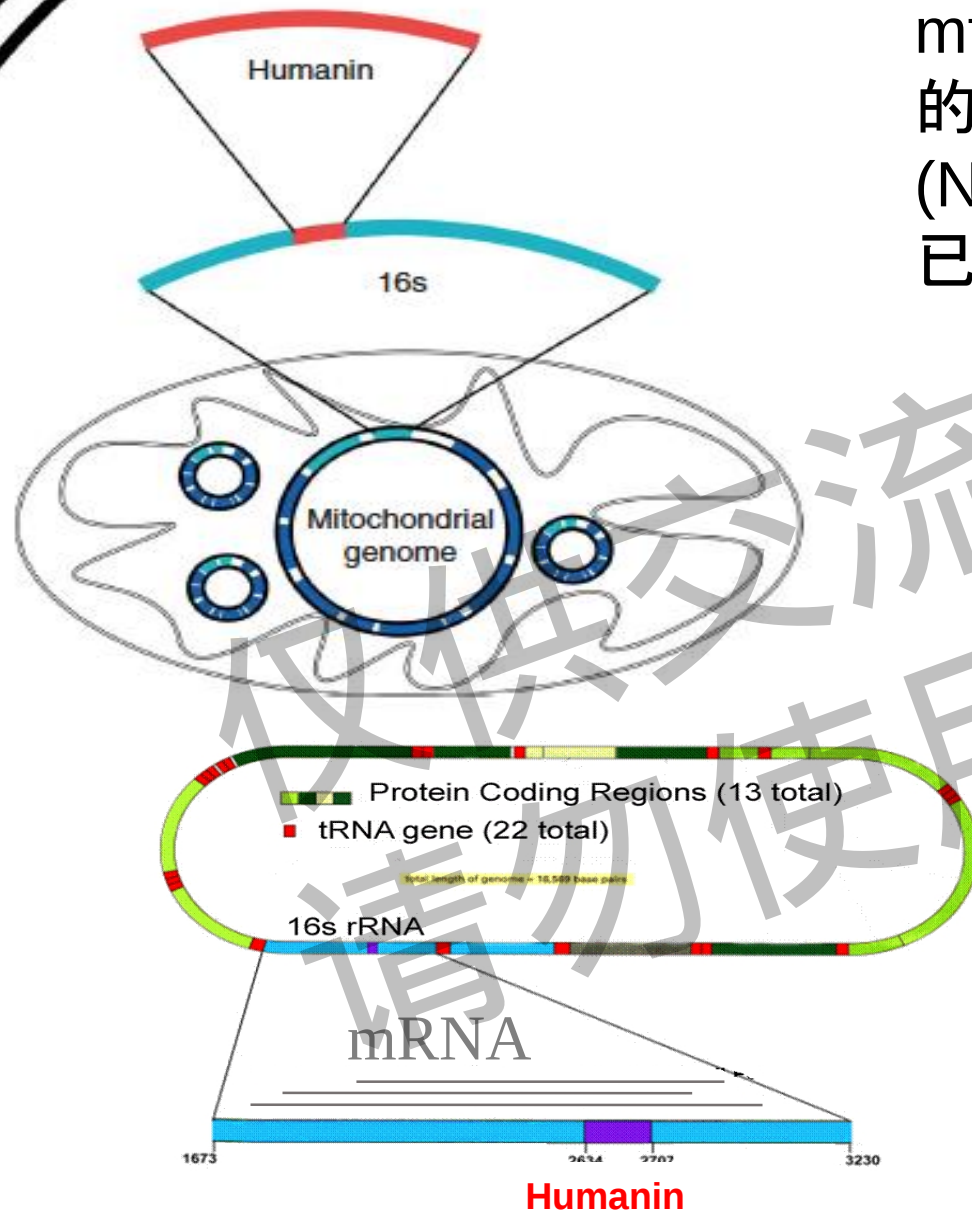


Humanin: 第一个被发现的线粒体多肽

mtDNA中的ORF在16S ribosomal RNA上转录的24个氨基酸的多肽

(Nature 2003) (PNAS 2001, 2003)

已被多个科研单位用不同的方法成功克隆



保守序列

- 生成多聚腺苷化的mRNA, 与rRNA不同并较rRNA短
- 在胞浆中翻译并分泌

由线粒体基因中的基因编码。高度保守存在于大脑、睾丸、CSF、血浆

细胞保护性/ 代谢保护性

表达水平呈年龄依赖性, 并与寿命、健康相关

Humanin SNP (rs2854128) 与Humanin表达水平下降及认知减退有关

nature > scientific reports > articles > article

SCIENTIFIC REPORTS

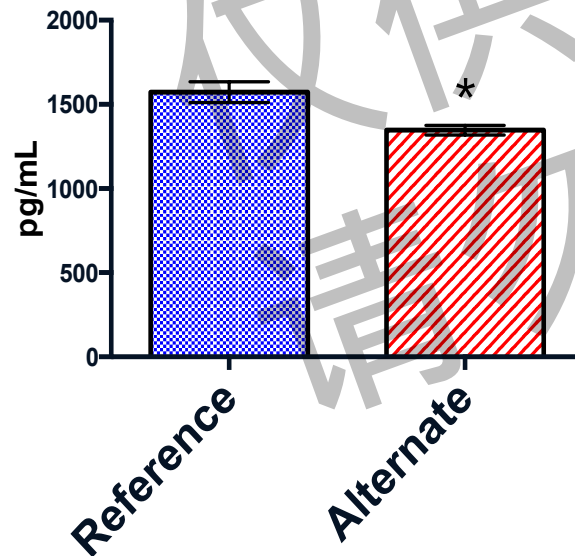
Article | OPEN | Published: 21 September 2018

Humanin Prevents Age-Related Cognitive Decline in Mice and is Associated with Improved Cognitive Age in Humans

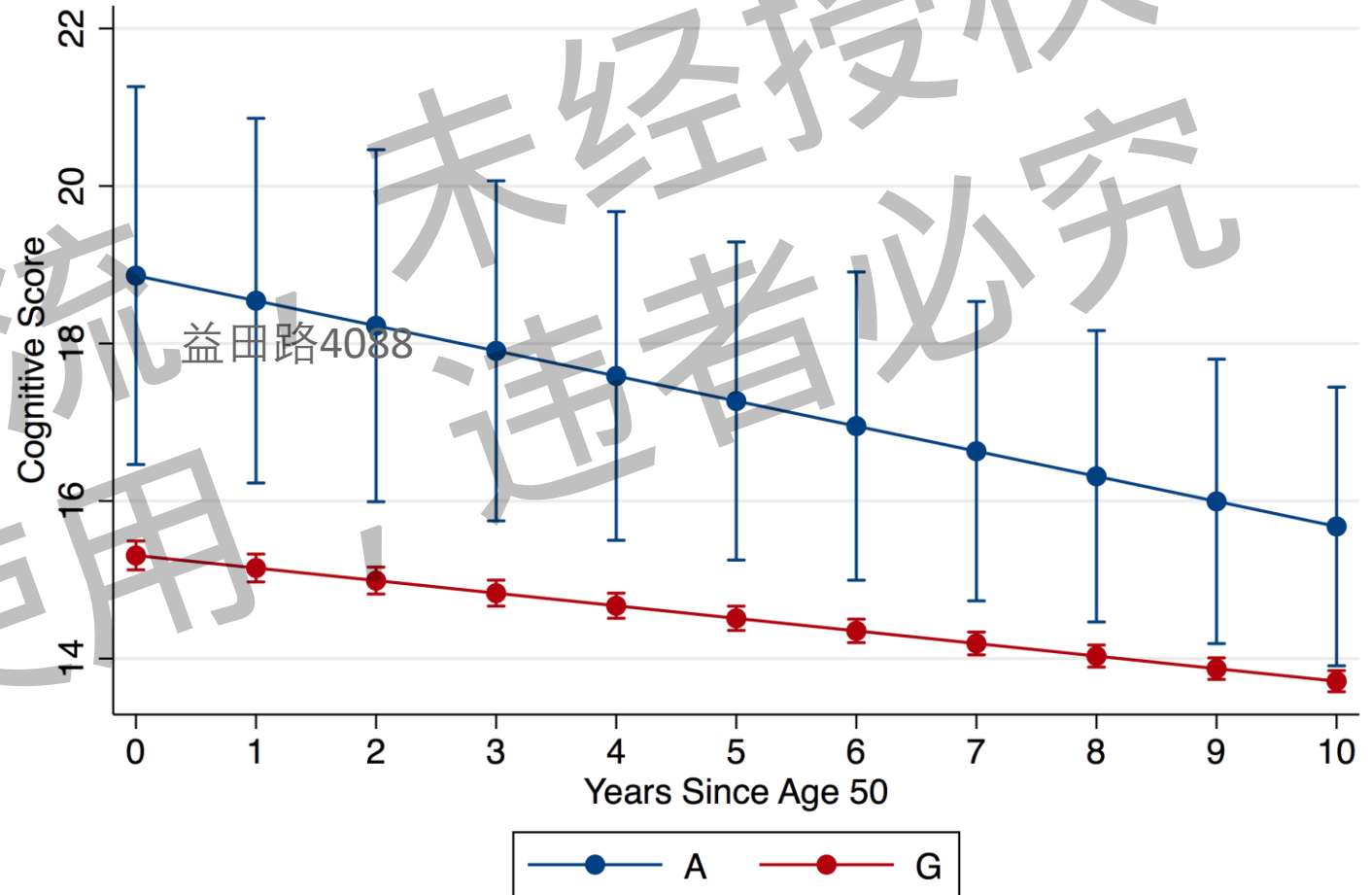
Kelvin Yen, Junxiang Wan, Hemal H. Mehta, Brendan Miller, Amy Christensen, Morgan E. Levine, Matthew P. Salomon, Sebastian Brandhorst, Jialin Xiao, Su-Jeong Kim, Gerardo Navarrete, Daniel Campo, G. Jean Harry, Valter Longo, Christian J. Pike, Wendy J. Mack, Howard N. Hodis, Eileen M. Crimmins & Pinchas Cohen

Sci

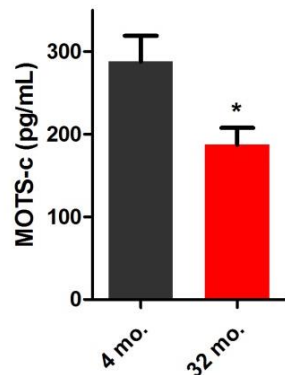
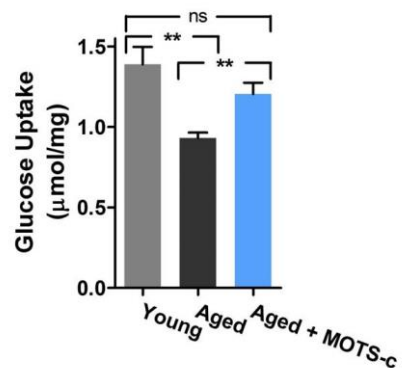
Circulating HN Levels



Effect of Humanin Allele on Cognitive Decline in AAs



MOTS-c 对饮食诱导的肥胖及脂肪肝具有预防作用



一种12S来源的
可以激活
AMPK的多肽

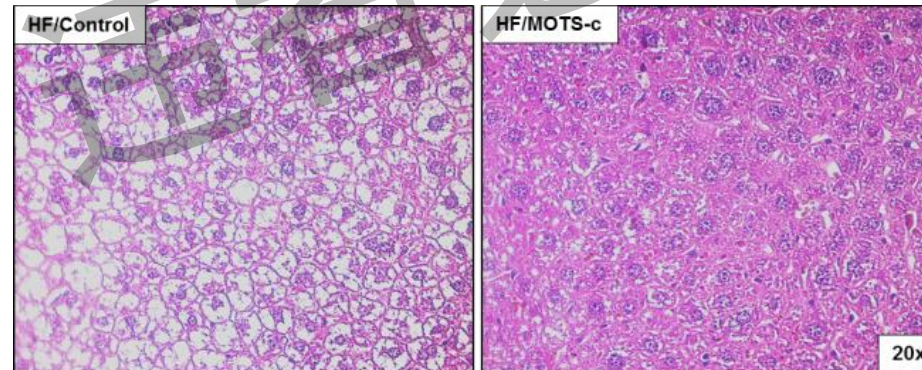
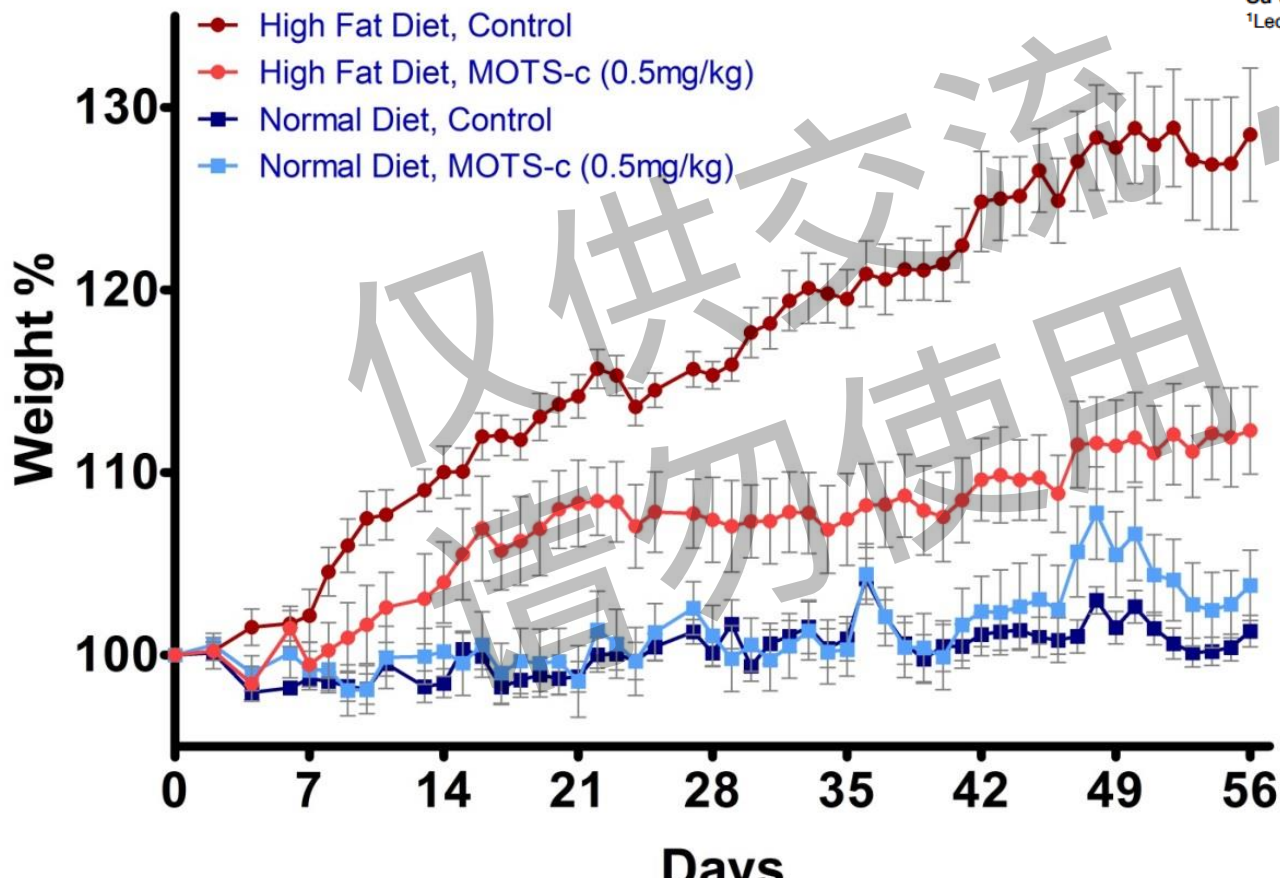
Cell Metabolism
Article

Cell
Metabolism

CellPress

The Mitochondrial-Derived Peptide MOTS-c Promotes Metabolic Homeostasis and Reduces Obesity and Insulin Resistance

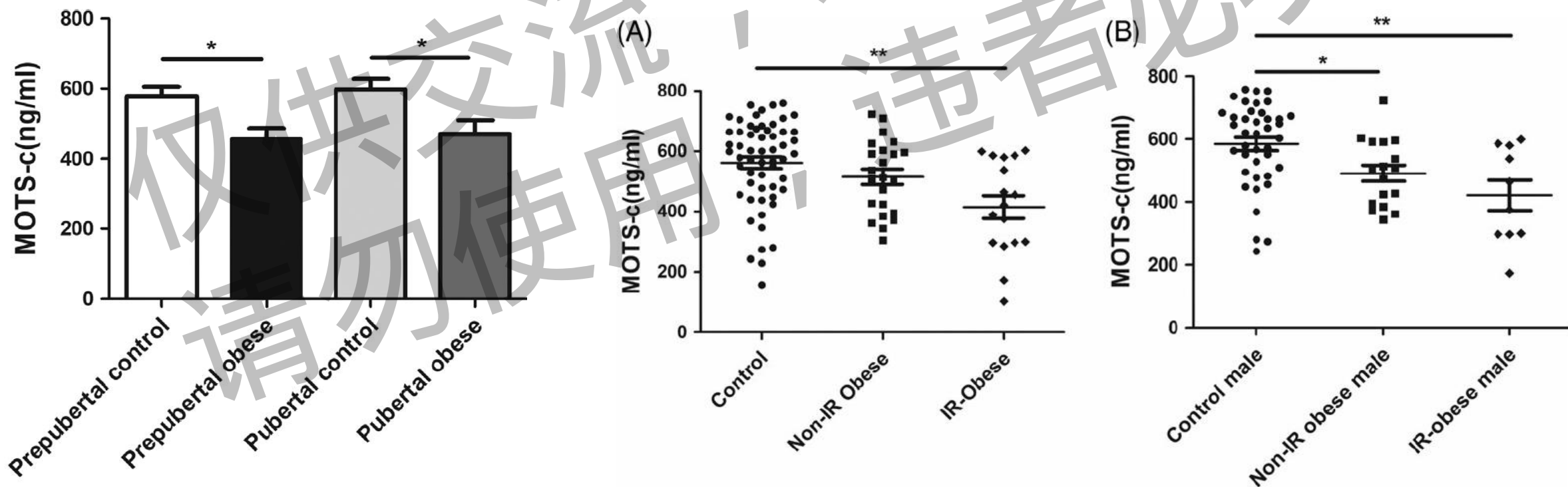
Changhan Lee,^{1,*} Jennifer Zeng,¹ Brian G. Drew,² Tamer Sallam,⁴ Alejandro Martin-Montalvo,³ Junxiang Wan,¹ Su-Jeong Kim,¹ Hemal Mehta,¹ Andrea L. Hevener,² Rafael de Cabo,³ and Pinchas Cohen^{1,*}
¹Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA



1期临床试验正在进行中

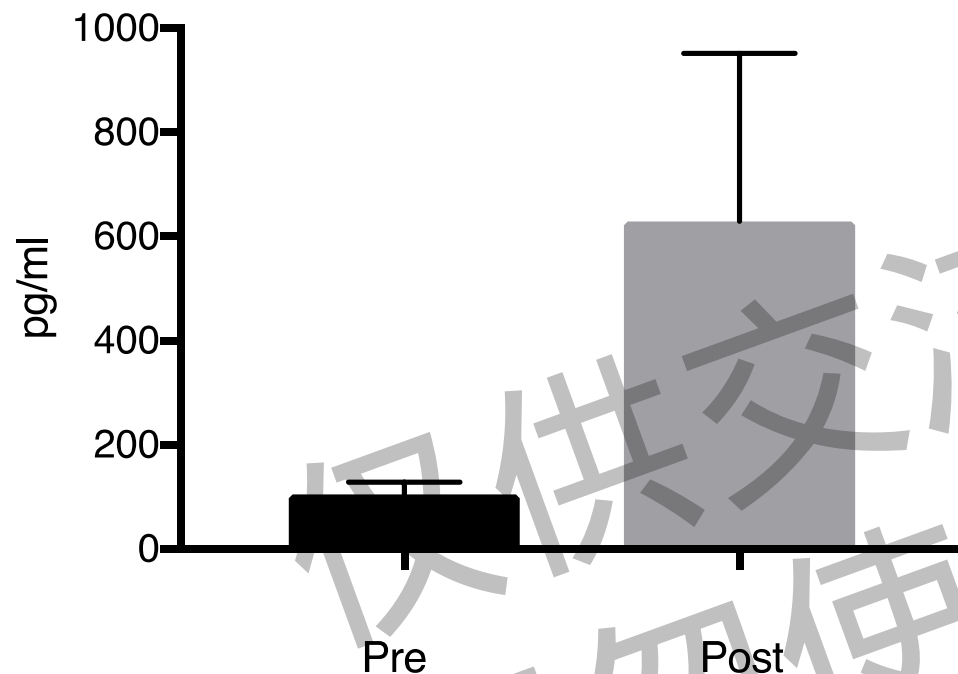
Circulating MOTS-c levels are decreased in obese male children and adolescents and associated with insulin resistance

Caiqi Du¹ | Cai Zhang¹ | Wei Wu¹ | Yan Liang¹ | Anru Wang^{1,2} | Shimin Wu¹ |
Yue Zhao¹ | Ling Hou¹ | Qin Ning³ | Xiaoping Luo¹

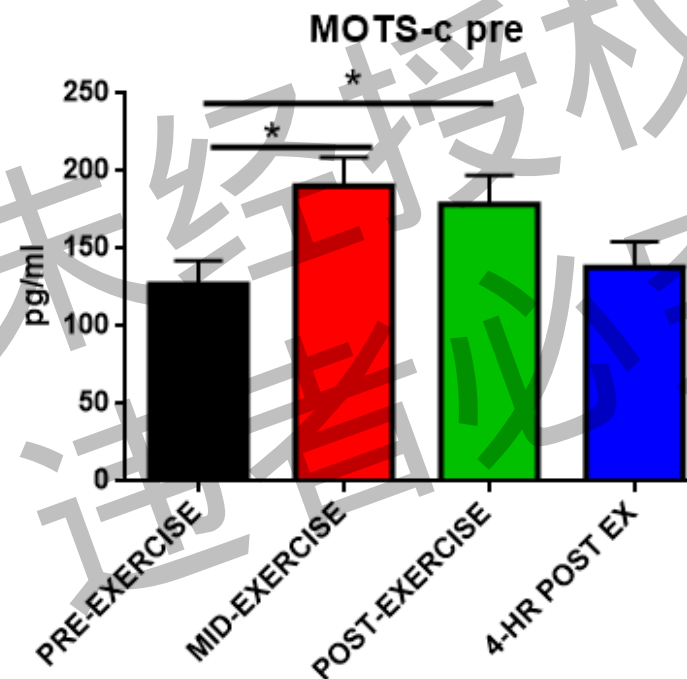


MOTS-c与运动相关

Effects of Exercise on plasma MOTS-c



3个月运动的效果

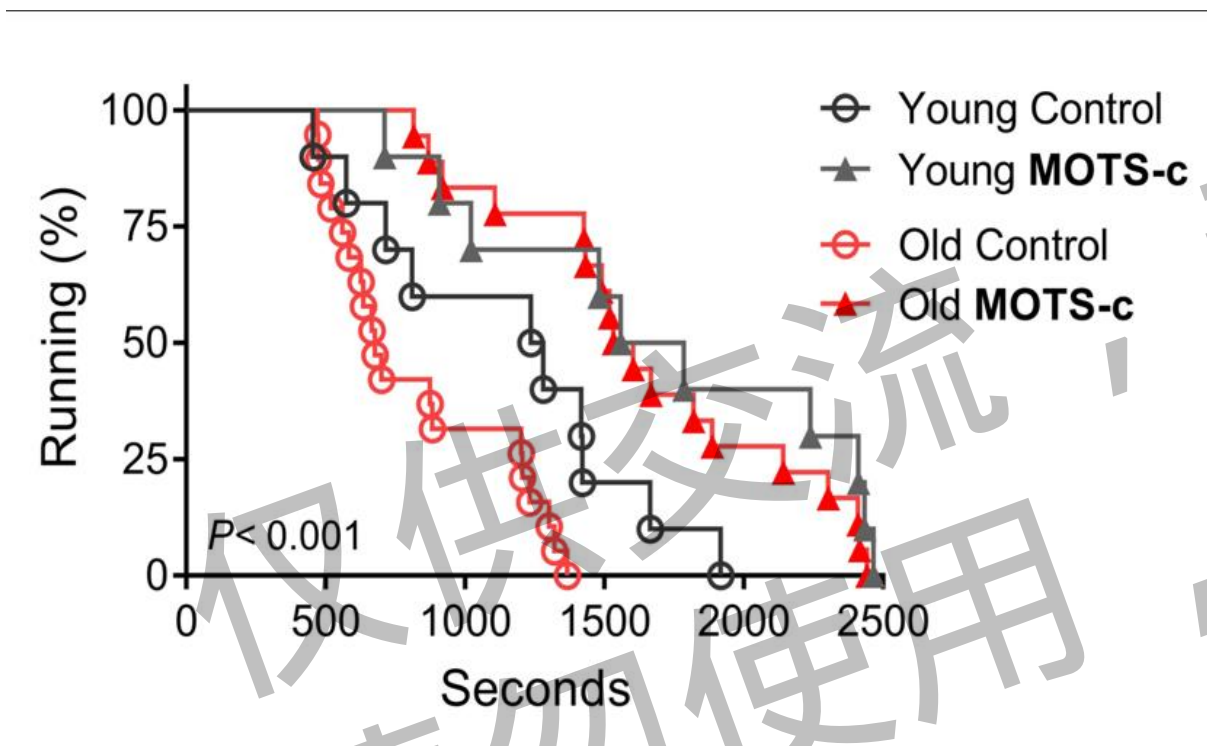


短期运动的效果

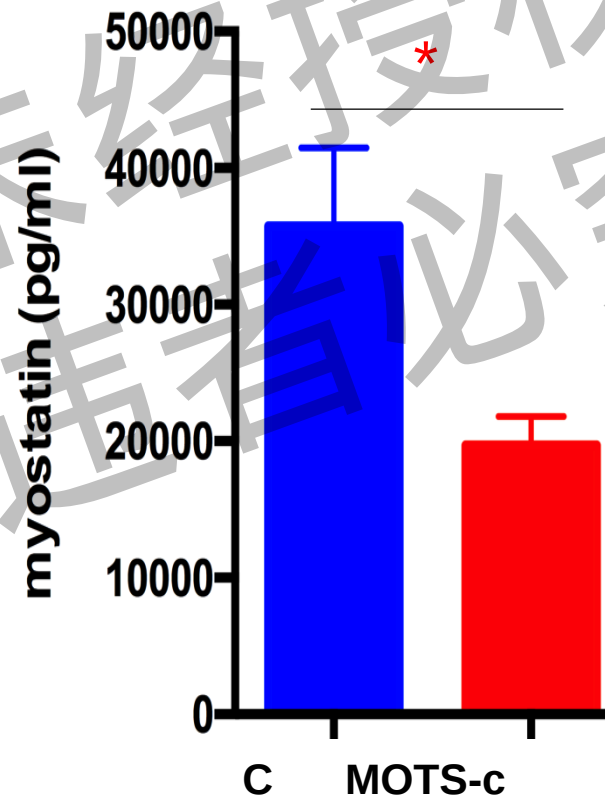
Comprehensive analysis of common and rare mitochondrial DNA variants in elite Japanese athletes: a case-control study

Eri Mikami^{1,2,3}, Noriyuki Fuku³, Qing-Peng Kong⁴, Hideyuki Takahashi⁵, Nao Ohiwa⁵, Haruka Murakami⁶, Motohiko Miyachi⁶, Mitsuru Higuchi⁷, Masashi Tanaka³, Yannis P Pitsiladis⁸ and Takashi Kawahara⁹

MOTS-c 与运动能力相关

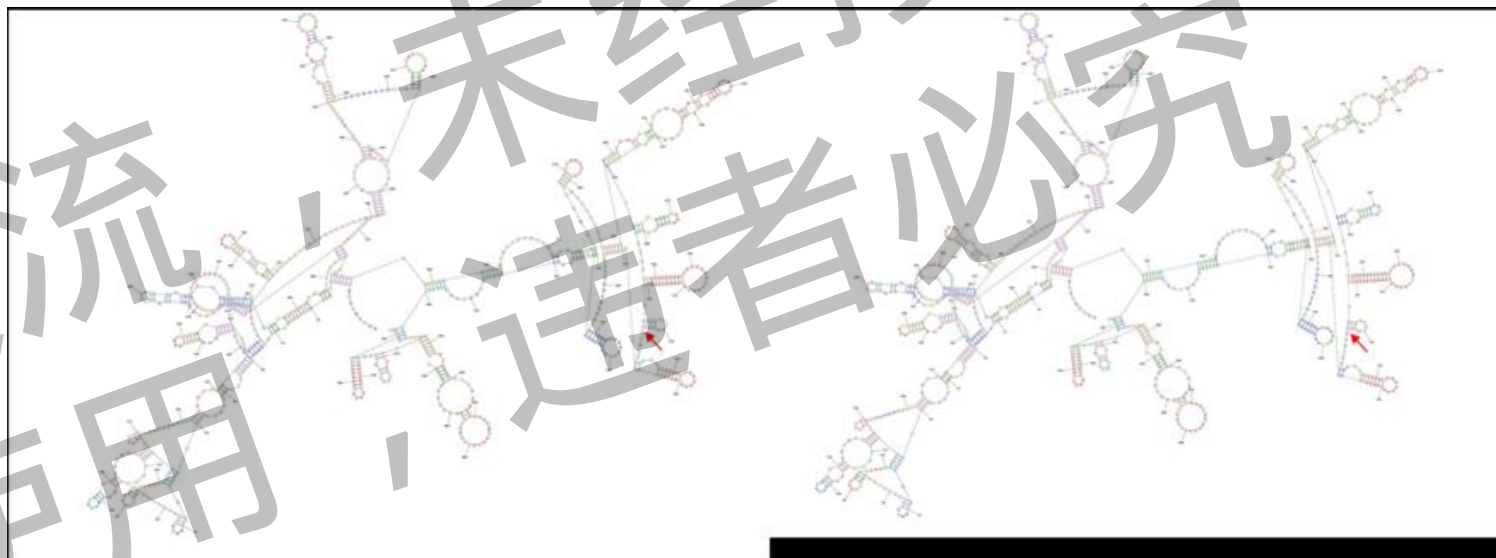


每日15-mg/kg MOTS-c 腹腔注射持续2周



2个月的治疗
对Myostatin
表达水平的
影响

mt1382A/C SNP -- MOTS-c K14Q
(SNP 只在7-9% 的北亚人中发现)
导致构象改变

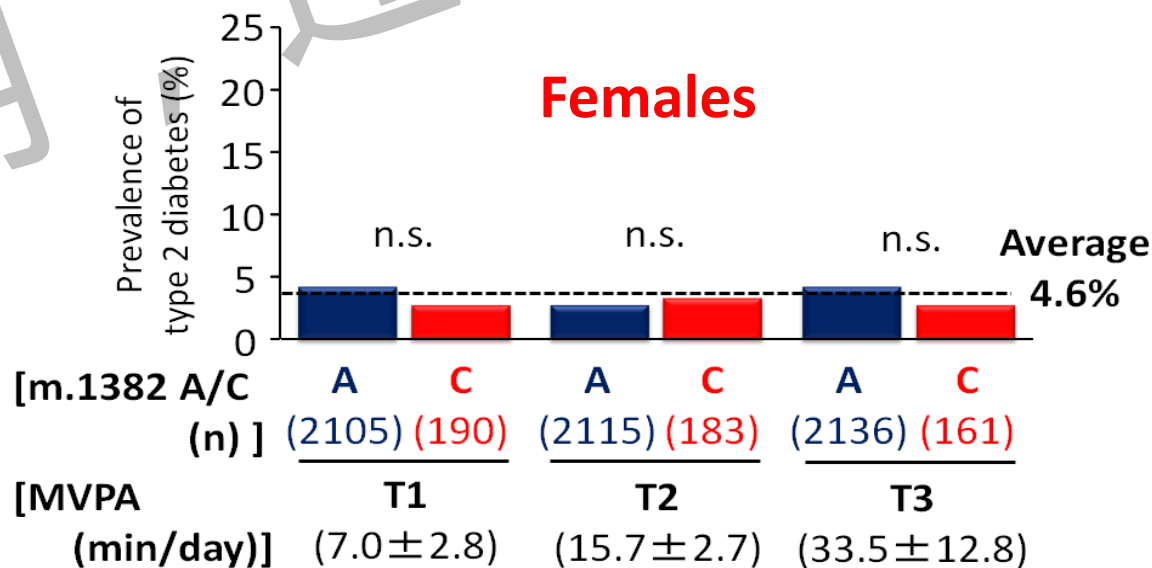
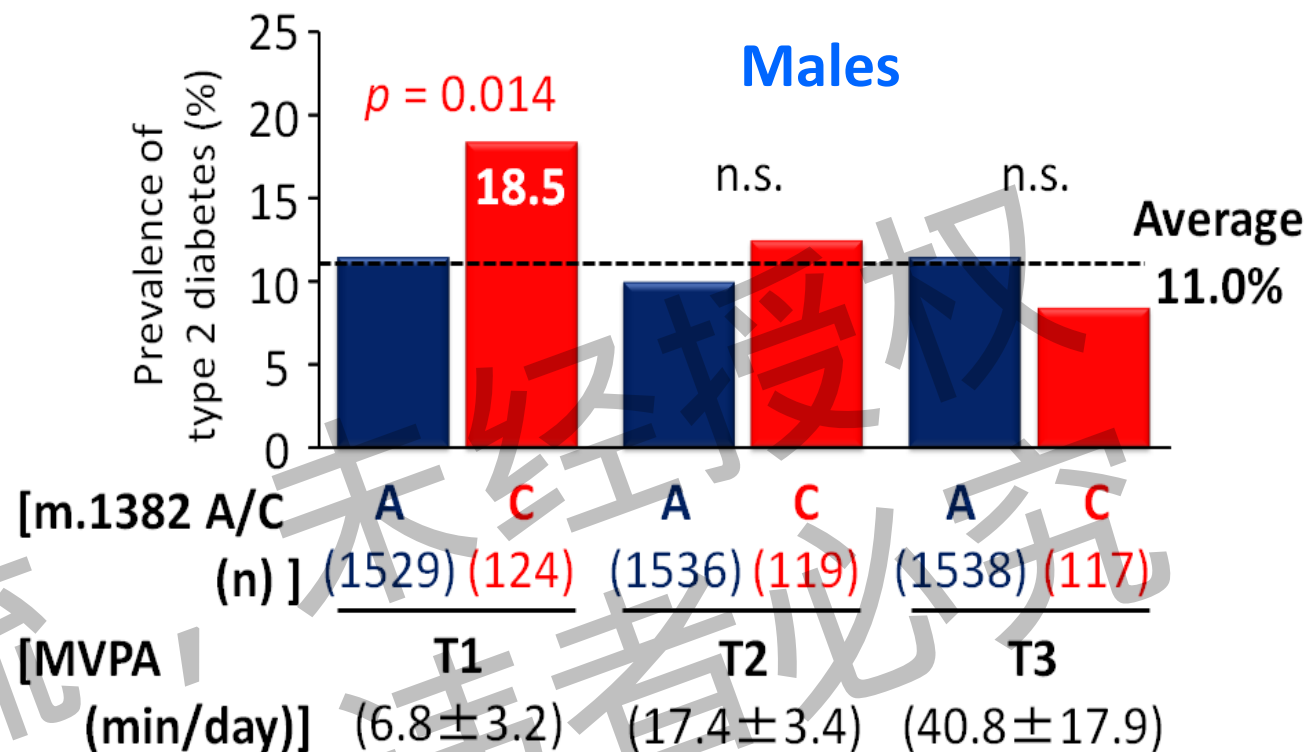


J-MICC研究

MOTS-c SNP与运动依赖的糖尿病高危因素有关

男性特异性运动基因组的相互作用

只有单倍群中的SNP参与T2DM

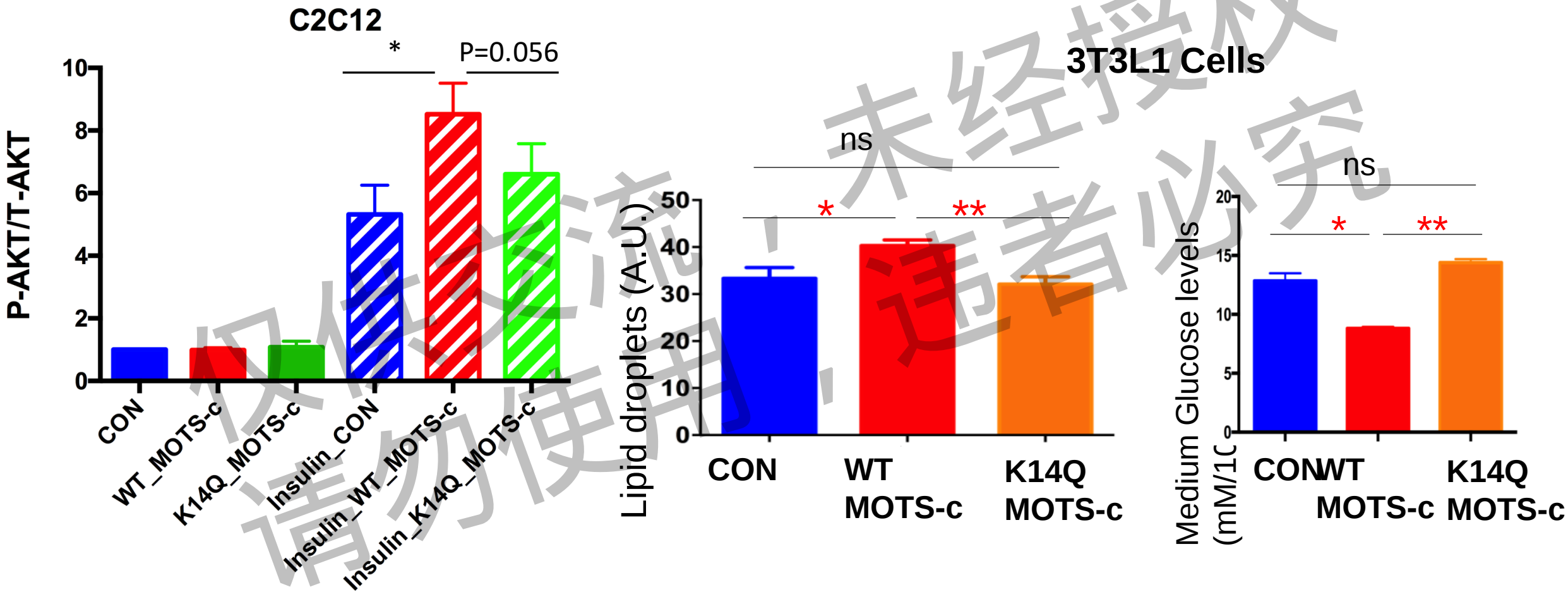


已在独立队列中验证 (MEC): 夏威夷的日本人

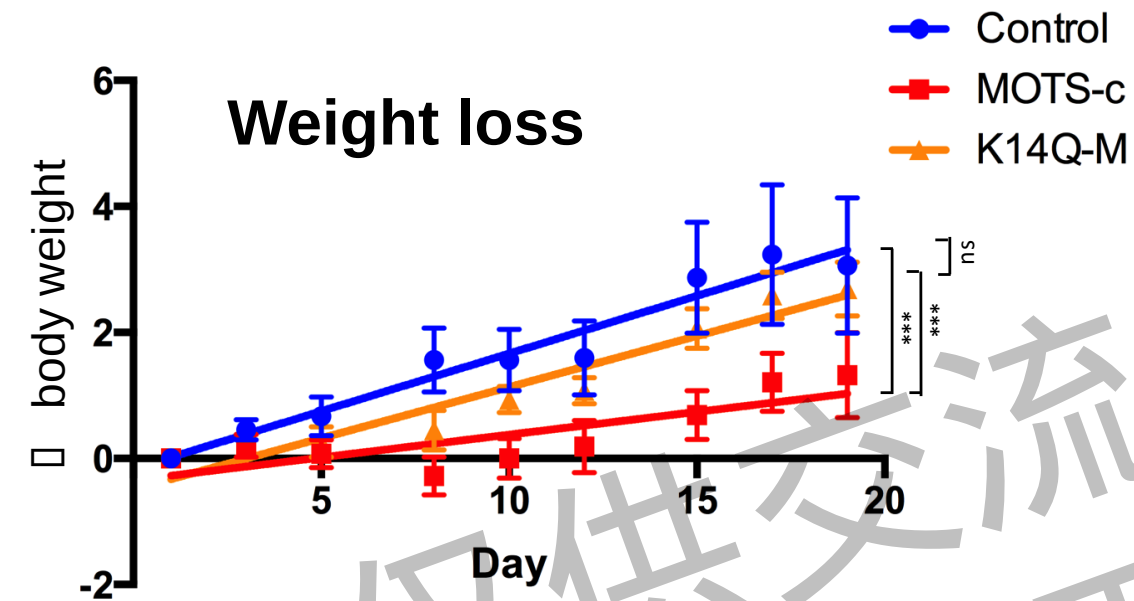
Association of exm2216209_C with T2D among PAGE MEC Japanese Americans - haploid analysis						
	N (Cases / Controls)	exm2216209_C Freq	Beta*	OR*	95% CI*	P-value*
Males	1810 (1,016 / 794)	0.076	0.3894	1.48	(1.01 - 2.15)	0.0424
Females	1577 (783 / 794)	0.068	-0.1880	0.83	(0.53 - 1.28)	0.4014
* The results above are adjusted for age, BMI						

实际上日裔美国男性比日本男性报告的剧烈活动少，强化了运动基因组相互作用的效果。

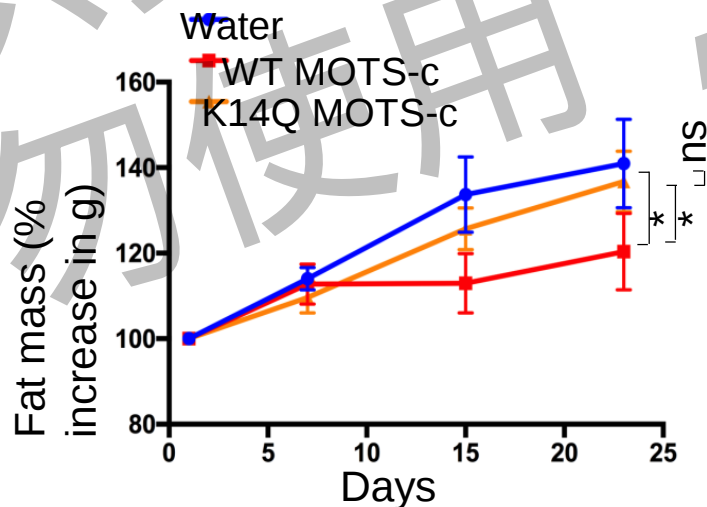
体外MOTS-c K14Q变异的作用较弱



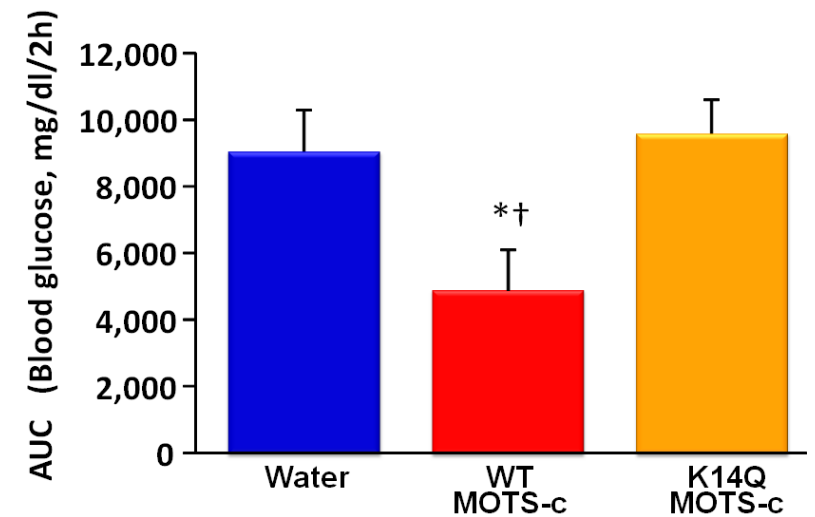
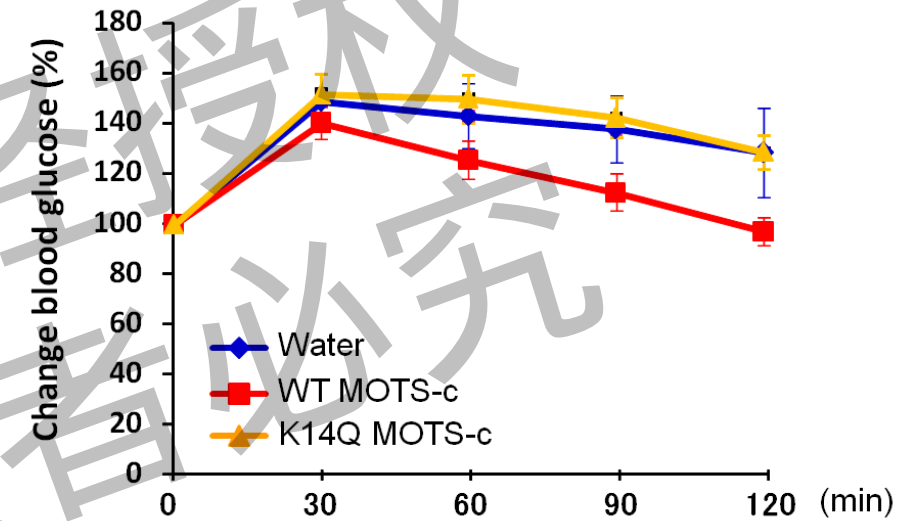
K14Q MOTS-c在雄性小鼠体内作用较弱



Fat Reduction



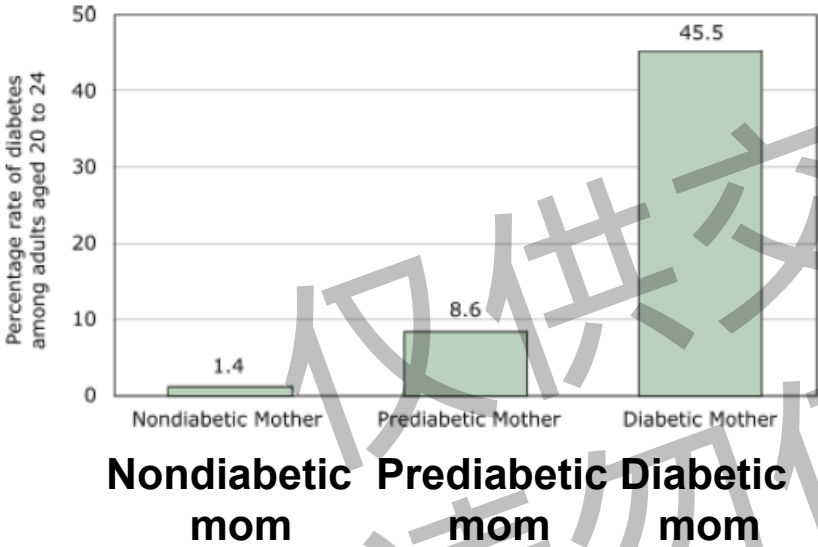
GTT



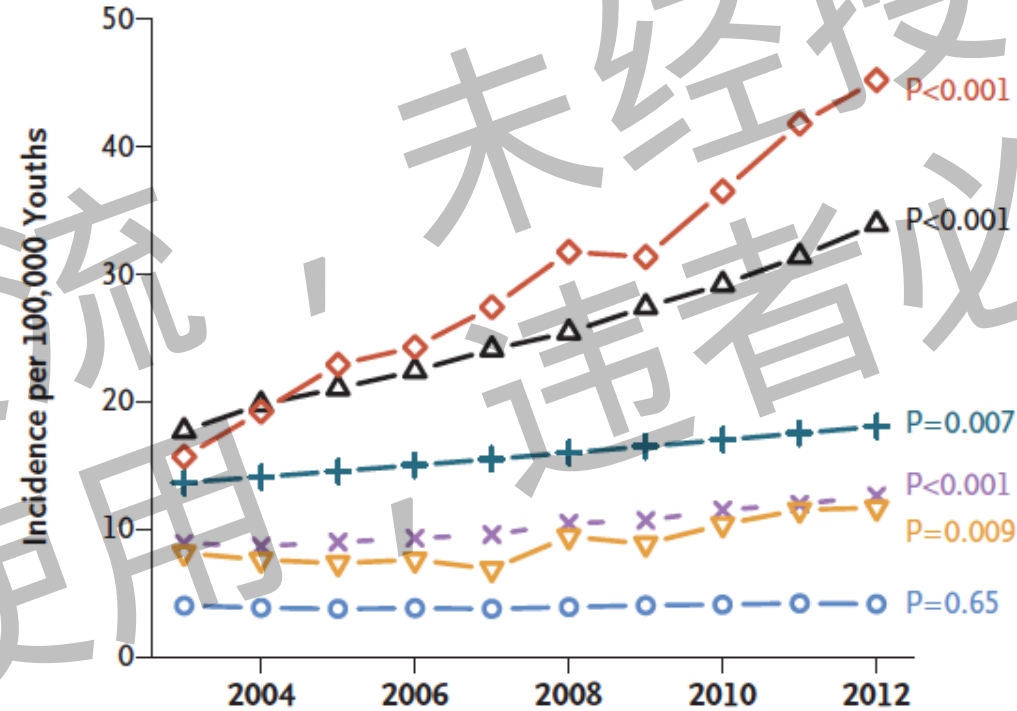
美国原住民的健康问题

生活方式, 饮食, 经济
肥胖, 糖尿病, 寿命减少

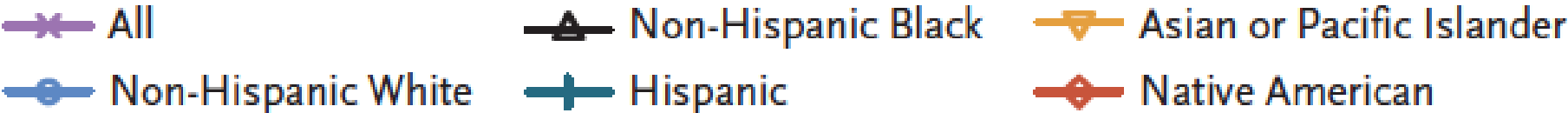
Prevalence of diabetes among Pima Indians age 20-24



B Type 2 Diabetes, 10–19 Yr of Age

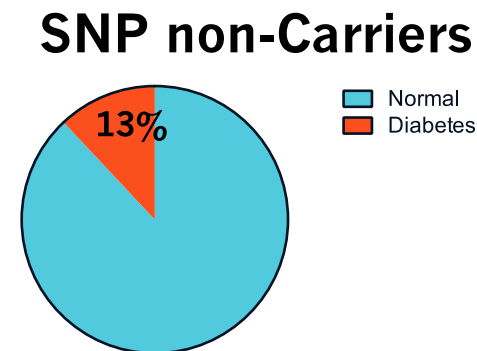
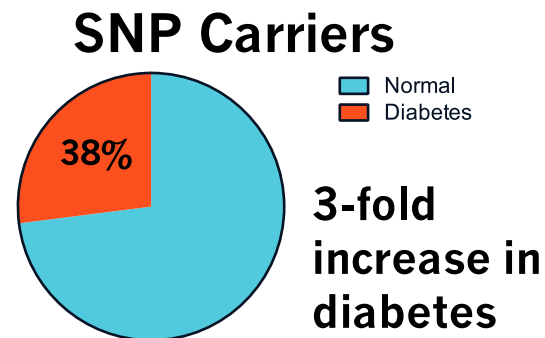
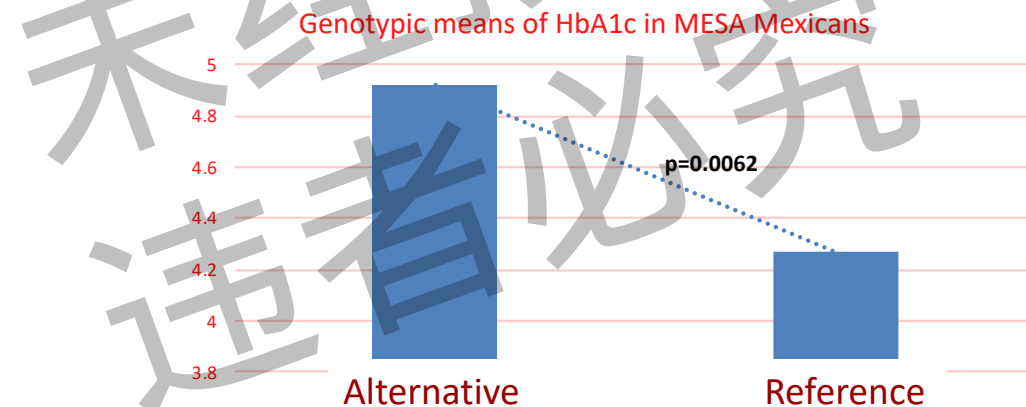
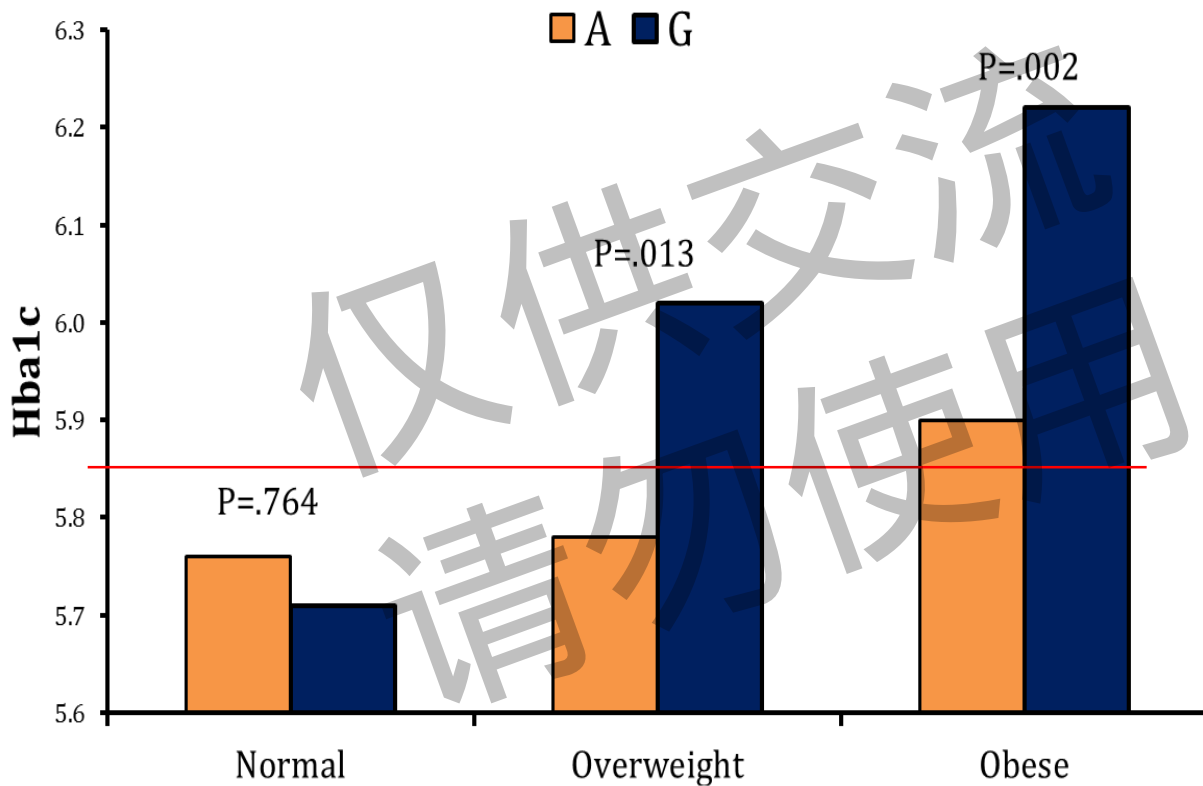


The NEW ENGLAND JOURNAL of MEDICINE



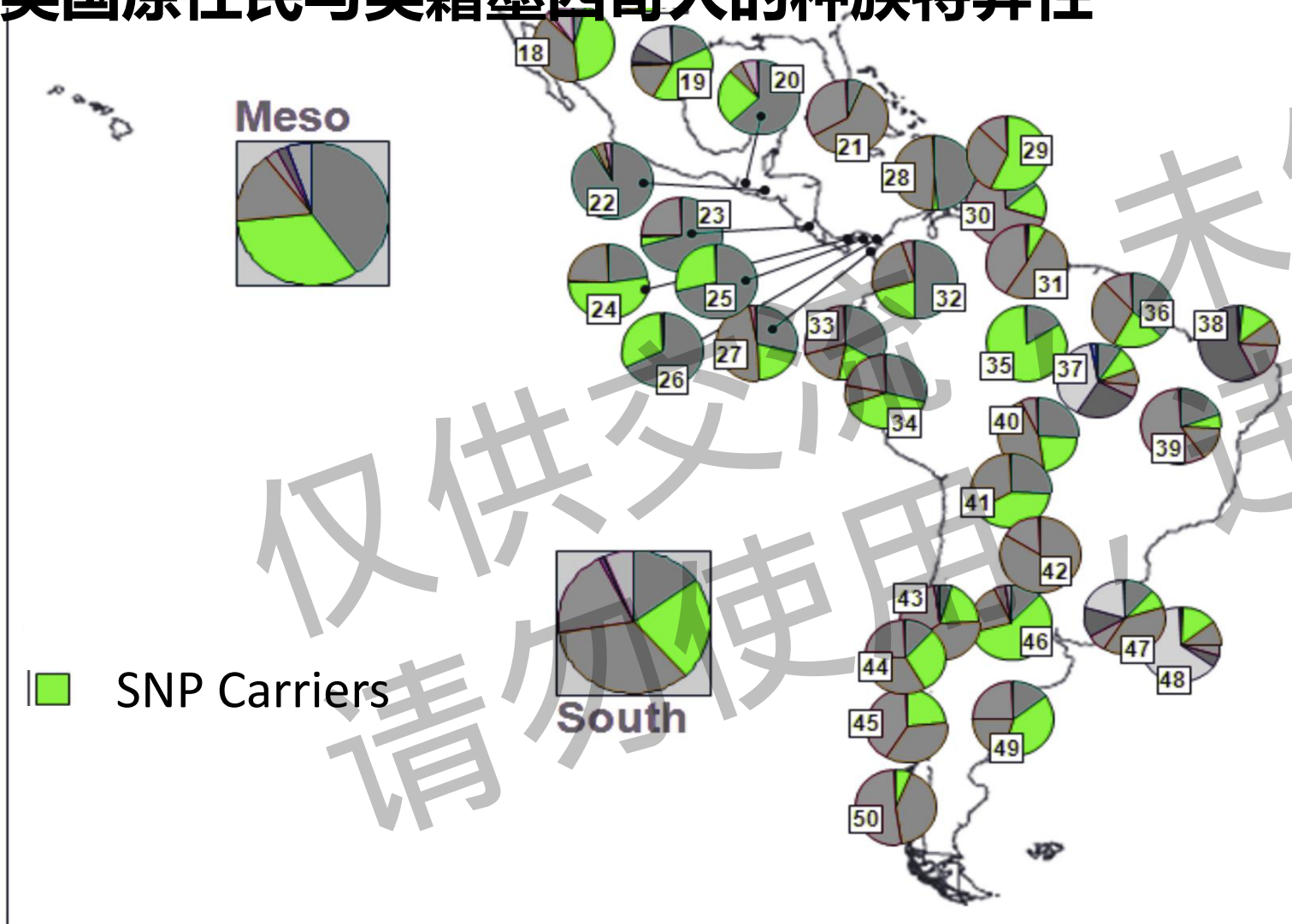
MENTSH基因的发现

在合并肥胖时可导致糖尿病易感的一种线粒体基因突变, (三倍风险)
Identified通过对健康及退休研究的MiWAS scan发现 (~20,000 研究对象)



美国人群中的SNP分布

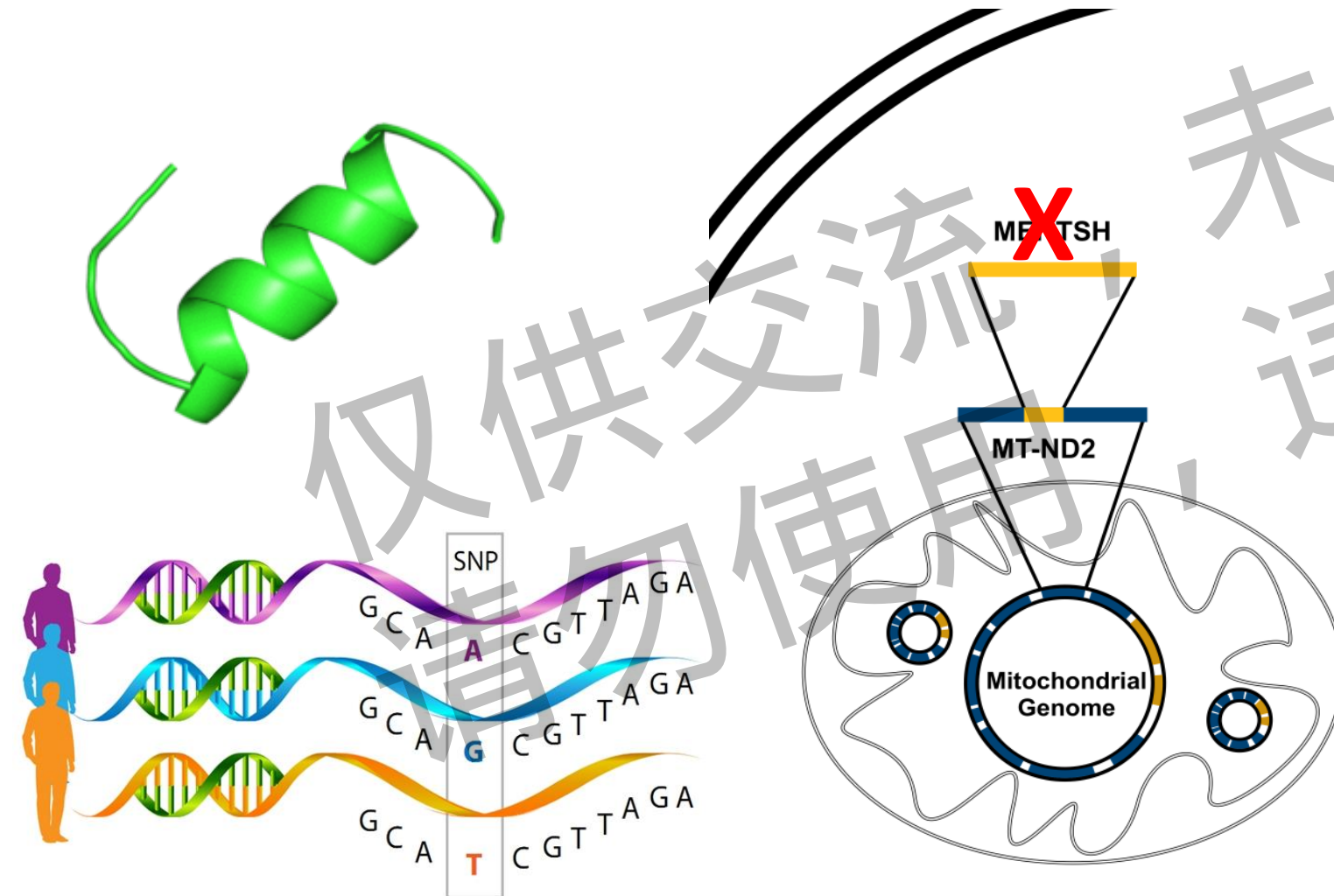
美国原住民与美籍墨西哥人的种族特异性



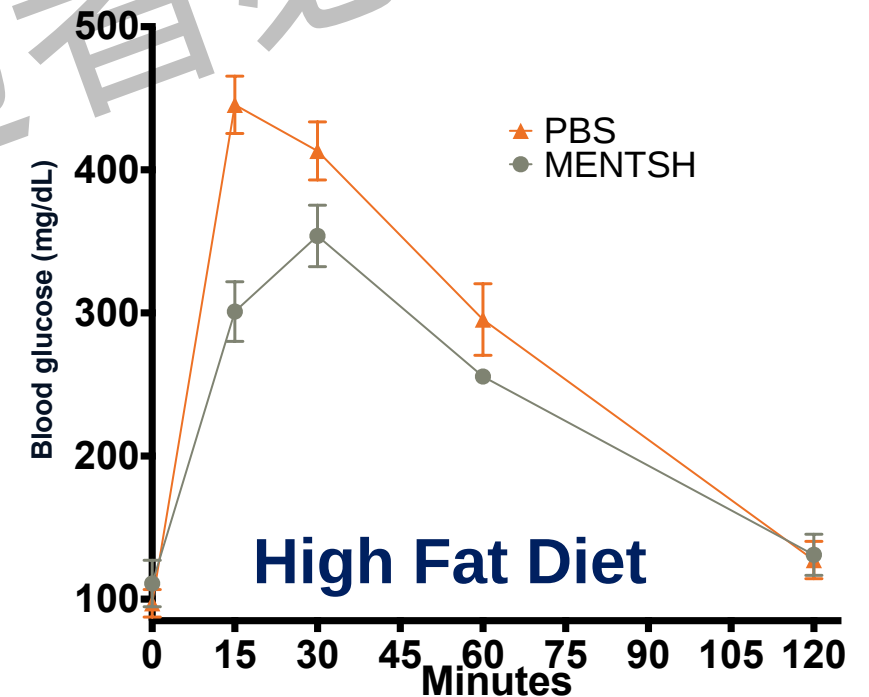
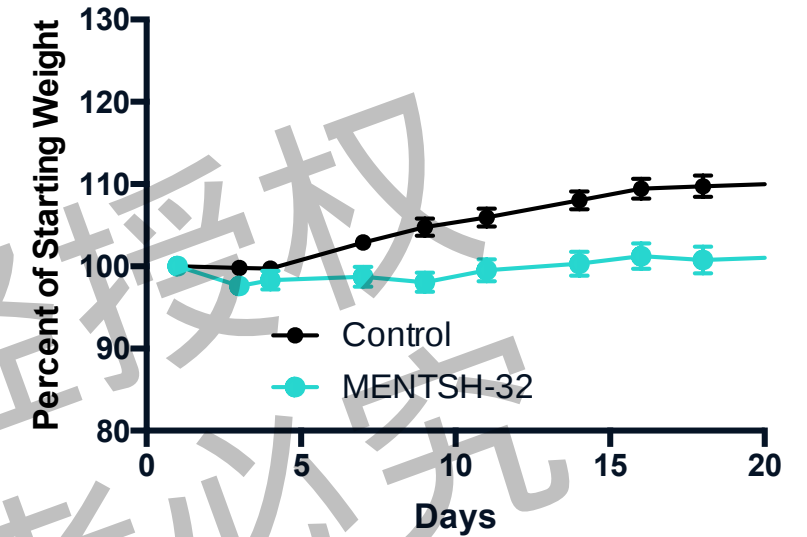
SNP在30-70%的美国原住民、>20%的墨西哥人中出现，但只在0.3%的拉丁美裔人中出现。SNP来源与美国原住民，普遍出现在美洲中部及南部。SNP在新多肽中消除了起始密码子。

MENTSH

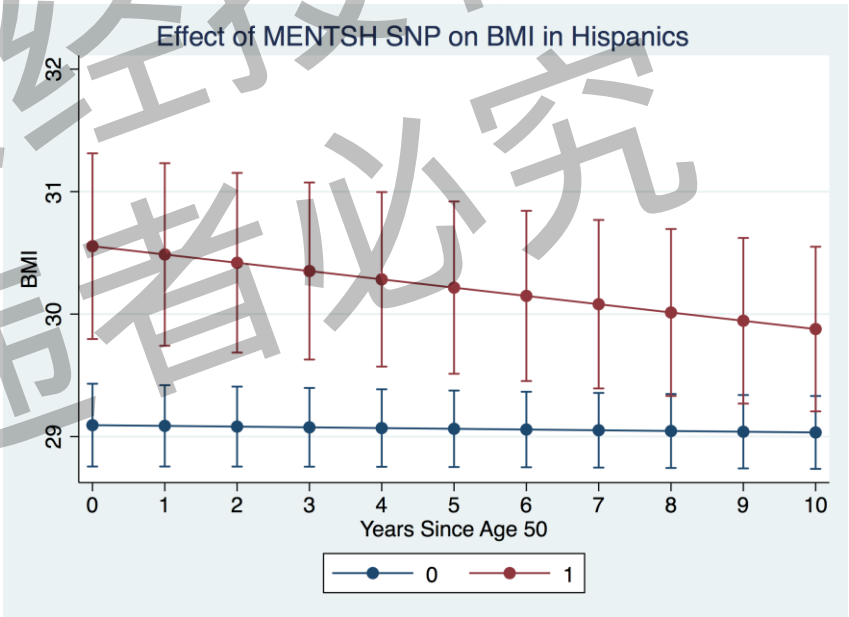
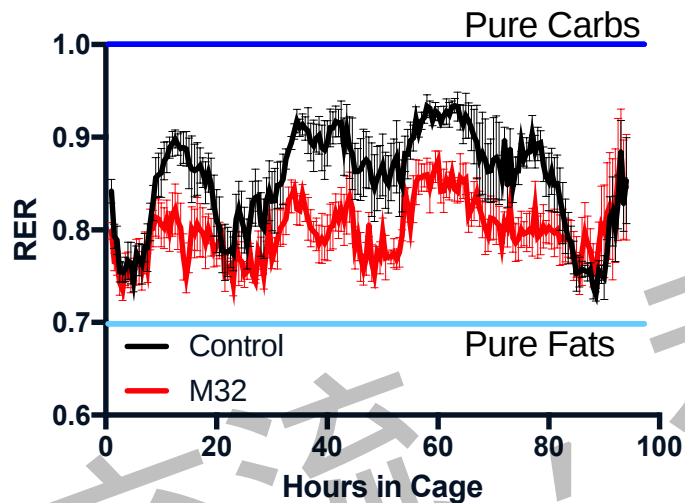
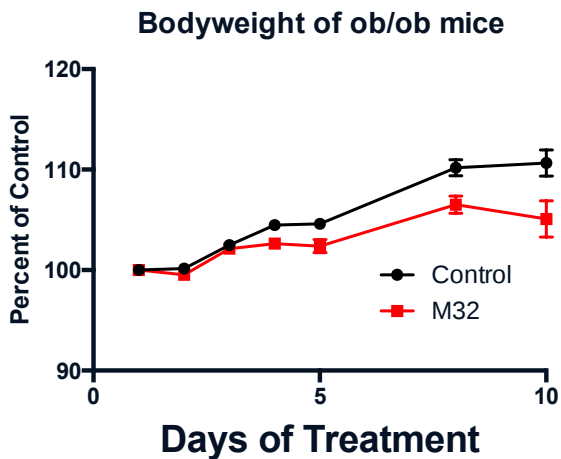
MDP Encoded in the ND Two Subunit of Humans



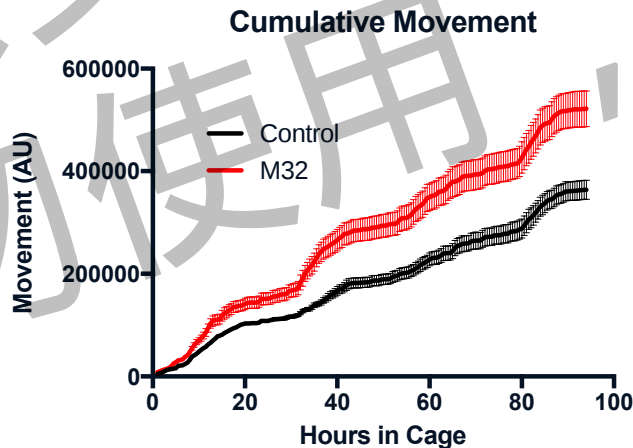
Body Weight



MENTSH影响脂肪代谢



Did not change food intake



Discovery and characterization of smORF-encoded bioactive polypeptides

Alan Saghatelian^{1*} & Juan Pablo Couso^{2*}

Mackowiak *et al. Genome Biology* (2015) 16:179
DOI 10.1186/s13059-015-0742-x



RESEARCH

Open Access

Extensive identification and analysis of conserved small ORFs in animals



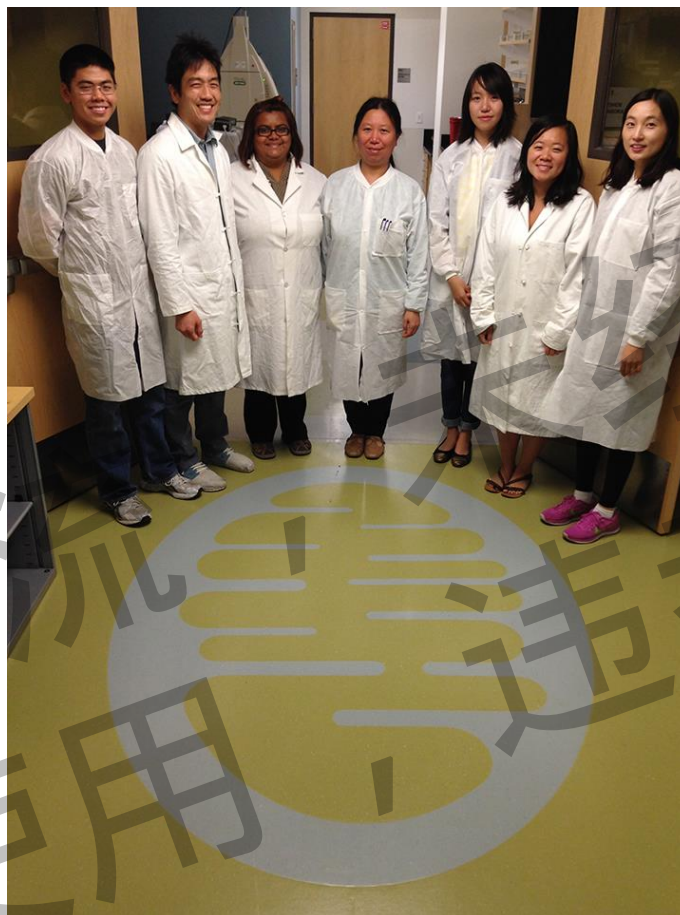
Sebastian D. Mackowiak¹, Henrik Zauber¹, Chris Bielow^{1,2}, Denise Thiel¹, Kamila Kutz¹, Lorenzo Calviello¹, Guido Mastrobuoni¹, Nikolaus Rajewsky¹, Stefan Kempa¹, Matthias Selbach¹ and Benedikt Obermayer^{1*}

MDPs – 线粒体来源多肽新家族- 是独特的线粒体信号

- mtDNA是衰老-运动领域中具有前景的研究方向
- MDPs作为代谢调节因子具有重要的功能
- **MDPs可DR模拟和运动模拟**
- **MOTS-c突变& 久坐生活方式可导致亚洲人的糖尿病**
- **MENTSH中的新SNP与美国原住民糖尿病相关**
- **MDP水平可被预测 & 有助于监测运动反应**
- **MOTS-c & 其它MDPs具有巨大的治疗前景**
- 更多的功能有待发现

感谢线粒体合作伙伴:

Noriyuki Fuku (Juntendo)
David Lee (USC)
Andrea Hevener (UCLA)
Valter Longo (USC)
Eileen Crimmins (USC)
Nir Barzilai (Einstein)
Amir Lerman (Mayo)
Morgan Levine (Yale)
Nick Musi (UTSA)
Nathan LeBrasseur (Mayo)
Troy Merry (U Auckland)
Wendy Setiawan (USC)



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Brendan Miller
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由以下Pinchas Cohen的基金共同支持:

2P01AG034906, DOD PC160353, AFAR BIG Award,
U54CA233465, R01AG061834, R01CA231219

可合作性提供我们的独有试剂,
包括转基因小鼠及实验方法等。