If I Were a First Year Graduate Student Now

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First of all, 首先我想提醒同学们：科学研究可以不仅仅是工作（job），it can really be fun，可能还是很好玩，拿好玩做工作，是privilege。

如果好玩，记住下面的没有坏处：

你是自己喜欢做研究

你为自己工作：你自己首先不必把研究认为是受人指挥、受人剥削，如果那样不如离开科学研究（我可不认为离开科学一定是贬义）

你没有老板/boss，也没有导师

你有PIs和advisors who can be your mentors and colleagues

如果你不是特别想做奴隶受剥削，那么你不要找奴隶主式的PIs/advisors

可以找一个你可以work with的人, 而不是work for 的人,找一个你喜欢的课题，使你的生活有趣

你的(研究)生涯最重要的决定人是你自己

"你为自己工作"的原则具体到这门课：

你自己负责

课前读文献

课中动脑筋、提问题

课后自己提高

课程给大家一个基础，各人自己花费的脑筋、功夫、和时间使各人得到的益处非常不同，如果你用以前小中大学的对付考试方法，不能对这门的的真正点心领神会自己发挥，效果就很小

去多一点问高年级同学，你会发现同是这门课出来的，花了功夫和没花功夫的结果大不一样，这样的课给你们提高自己能力的机会，以前你们的课多半大家水平不太容易区分。这门课实际结果是你们可以看到同学的差别是很大的（先在一两年内显现，后在长期显现）

如果你真体会到，这门课是很重的，不过没有人压你，如果你只关心应付考试，你可以把他浪费掉，因为考试对你学到这门课的精髓是不太重要的

第二, 我希望你们自己能够 shake a few assumptions and presumptions imposed on you by teachers from your

kindergartens
primary schools
middle schools
colleges

who, although having no direct knowledge or knowledge of real or good research, gave you stereotypes of scientists or reasons underlying successes in scientific research

你们需要自己重新看待和直接体会科学研究

Partly to have an shock and awe effect, partly supported by experiences (yours and mine with the Chinese education system and cultural environ), I am going to claim that most (albeit not all) of your teachers were teaching you stereotypes without really knowing how science actually progresses and how scientists really carry out research

听老科学家的不是牢靠的保证：有些有益有些可是有害

考试成绩和研究能力没有绝对关系

"聪明"在小时候突出和一生科学成就也无一定关系

你们一般听说的牛顿、居里的故事许多点都不是真的，有些可以说是哄小孩的、有些是当事人给自己编的、有些是不懂研究的人想像出来的

研究里面有许多不确定因素，使得总结可以"教导"人们"成功"很难，如果不是不可能的话

{事后讲故事不难（大家都差不多），事前就完全不同(给原来会用一般原理"教导"你的人一个没有完成的过程，试试看)}

…… … … … … …… …

对不同的同学来说

即可以是

坏消息

如果你的小中大学老师说你从小他们就认为"聪明"

也可以是

好消息

如果你的小中大学老师或者父母

说你不是他们认为做优秀科学家的材料

希望给你所谓压力来鼓励成才

他们都可以是对科学研究懂的不透彻，而且对你理解不深入，还看你自己判断，你自己做了

你的将来在你自己，不在过去人给你强加的结论

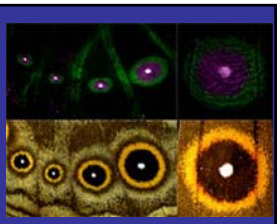
如果我现在是一年级研究生，

我希望做无论做多久研究、不管自己进展是否顺利(or perhaps especially when it is frustrating)，会记住生命科学研究

吸引我们大家的一些特点

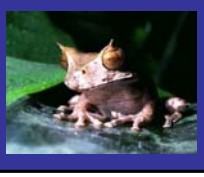
我们研究的对象是美丽的

Oh, I meant that
科学研究的结果可以是很漂亮的



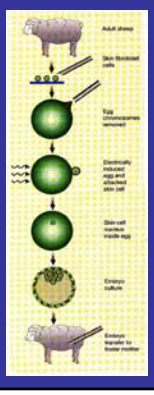
Sean Carroll at Wisconsin

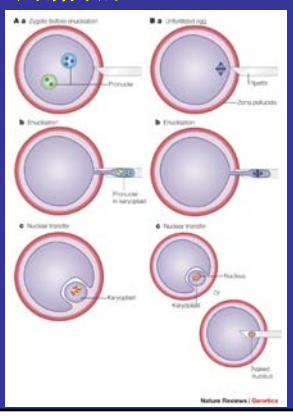
有趣的 often quite interesting and sometimes even fascinating



令人好奇的
curious
and sometimes
mysterious

有应用潜力的





And, yes, it does not hurt that

生命科学研究

underlie all diagnostic and therapeutic strategies
is essential for progresses in agriculture
is the basis for pharmaceutical industry
is the pillar of biotechnology

Now, 如果我这堂课就这样念标语喊口号（象那….一样），你们和我都肯定在
浪费时间
我怎么办呢?

讲一些故事，你们可以get exposed to a varieties of 真的或者接近真的研究课题和过程，
从中，你们每个人可以看你们能得到什么
我选的故事都有个人偏见，
（不过哪个人讲故事、写书，又没有偏见呢？）

我得说明
（听众中的）天才（也许定义就是）可能不需要学习，不过有点 exposures 也许不会损害他们，至少不是不可逆地损害他们

多数人, 从历史从他人那里学一点是必需的，至少进化看来是选择说学习是有利于"适"的. After all, that is why spoken language, writing, and formalized schools come about,
So a bit of stories may not be bad for you here today when you start your first graduate school class in the life sciences

我为什么讲这些故事

1) Well, 我被分配来教第一堂课，引论？
2) 有时有同学和其他人问我如何选择课题（或者研究策略）
那难的很，我不敢公开讲（洋相的可能太大）That is very difficult
3) 偶尔还有人让我预计多少年甚至下一世纪科学未来突破（或者更糟糕的是） 中国机构要搞计划，找突破点未来科学
我知道这肯定不可能，从来不答应That is impossible for me or anyone else (the conventional ones are known to most and re-telling is a waste of time; the truly exciting discoveries can not be predicted, almost by definition)
Anyone answering to such requests in the public has my sympathies because runs a big risk of showing his/her ignorance and/or making a fool of him-/her-self
(--private speculations not included here)

我为什么讲这些故事

但是讲过去的故事可以，如果有人能从过去的故事里面帮助自己计划自己的生涯，或者自己冒险预计或者大胆设计突破点，
或者没有直接作用，但是体会到某种精神
那都是好事
（不要都同意我的体会——我常常错，是要依赖你们自己体会）

我选择故事的大体标准

我喜欢的（偏心肯定有）

如果工作已经得了 Nobel 奖, 那我在这里讲的可能性减小，但不完全排除
有些故事是因为其发现重要 (and not surprisingly, likely to win Nobel prizes) (caution: I do not advocate that 不想做元帅的士兵不是好士兵，I understand why some believe it, but I am incline to believe that too much ambition is not necessarily good for 每一个科学家的科学，it is definitely not good for the happiness of all scientist)

有些因为有趣 interesting or elegant, even though they may never win anyone Nobel prizes (多数人并不会得 Nobel 讲，但是可以享受科学 anyway, but we can still have fun with science)

How I selected these stories （继续）

some can be significant in science and elegant in experiments and useful as a technology (and helpful to the scientist(s) in more than one ways

选的故事

来源的领域多半本课其他老师不讲的

尽量是近来的研究或者研究的importance/elegance 最近 (甚至今年)才认识或者充分体会到

there is neither fixed style nor 处方for 研究的成功 不同性格的科学家以不同的styles做出

不同时代的例子

可以是创造性的课题设计:
Meselson and Stahl （五十年代）
Nusslein and Wieschaus （七一八十年代）

可以是沿前人某个发现继续:
Krebs and Fisher （附Cori夫妇） （五，六十年代）

可以是为了解决重要问题
Roger Tsien （钱永健）和 Fura-2 （八十年代）
（附：Richard Tsien 钱永佑）

可以是自己好奇：
Prasher和GFP （九十年代）

Nicole Le Dourin
从法国中学老师到
世界著名发育生物学家

Chance and the Prepared Mind

What if you run into (or learn about) odd findings accidentally

sense and antisense RNA preparations are each sufficient to cause interference

(Fire et al.: *Development* **113**, 503–514, 1991
Guo & Kemphues: *Cell* **81**, 611–620, 1995)

interference effects can persist well into the next generation, even though many endogenous RNA transcripts are rapidly degraded in the early embryo

(Seydoux & Fire, *Development* **120**, 2823–2834, 1994)

odd and accidental findings

Fire, A., Albertson, D., Harrison, S. & Moerman, D. Production of antisense RNA leads to effective and specific inhibition of gene expression in *C. elegans* muscle. *Development* **113**, 503–514 (1991).

Guo, S. & Kemphues, K. *par-1*, a gene required for establishing polarity in *C. elegans* embryos, encodes a putative Ser/Thr kinase that is asymmetrically distributed. *Cell* **81**, 611–620 (1995).

Fire, A., Albertson, D., Harrison, S. & Moerman, D. Production of antisense RNA leads to effective and specific inhibition of gene expression in *C. elegans* muscle. *Development* **113**, 503-514 (1991).

MRC Lab of Molecular Biology, Cambridge, England.

We have used an antisense strategy to effectively disrupt the expression of two genes encoding myofilament proteins present in C. elegans body wall muscles. DNA segments from the unc-22 and unc-54 genes have been placed in reverse orientation in vectors designed to produce RNA in body wall muscles. When the resulting plasmids are injected into oocytes, progeny with defects in muscle function are produced. These animals have phenotypes consistent with reduction and/or elimination of function of the gene to which antisense RNA has been produced: twitching and disorganization of muscle filaments for the unc-22 antisense constructs and lack of muscle tone, slow movement, and egg laying defects for the unc-54 antisense constructs. A fraction of the affected animals transmit the defective muscle trait to subsequent generations. In these cases the transforming DNA is present at high copy number and cosegregates with the observed muscle defects. We have examined several of the unc-22 antisense plasmid transformed lines to determine the mechanistic basis for the observed phenotypes. The RNA product of the endogenous unc-22 locus is present at normal levels and this RNA is properly spliced in the region homologous to the antisense RNA. No evidence for modification of this RNA by deamination of adenosine to inosine was found. In affected animals the level of protein product from the endogenous unc-22 locus is greatly reduced. Antisense RNA produced from the transforming DNA was detected and was much more abundant than 'sense' RNA from the endogenous locus. These data suggest that the observed phenotypes result from interference with a late step in gene expression, such as transport into the cytoplasm or translation.

RNA populations to be injected are generally prepared using bacteriophage RNA polymerases. These polymerases, although highly specific, produce some random or ectopic transcripts. DNA transgene arrays also produce a fraction of aberrant RNA products. From these facts, we surmised that the interfering RNA populations might include some molecules with double stranded character. To test whether double stranded character might contribute to interference, we further purified single stranded RNAs and compared interference activities of individual strands with the activity of a deliberately prepared double stranded hybrid.

Fire et al., *Nature* **391**, 744- 745 (1998)

Andrew Fire, Siqun Xu, MARY K. MONTGOMERY*, STEVEN A. KOSTAS*†, SAMUEL E. DRIVER‡ & Craig C. Mello, February 19, 1998

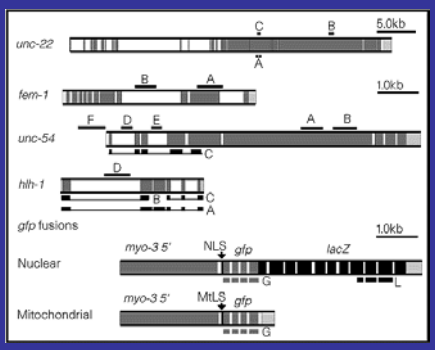
double-stranded RNA was substantially more effective at producing interference than was either strand individually.

evident in both the injected animals and their progeny.

only a few molecules of injected double-stranded RNA required per affected cell, arguing against stochiometric interference with endogenous mRNA and suggesting that there could be a catalytic or amplification component in the interference process.

Nature **391**, 744- 745 (1998)

Effective on Multiple Genes



New Biology

We do not yet know the mechanism of RNA mediated interference in *C. elegans*.

but

A simple antisense model is not likely

post-transcriptional:

dsRNA segments corresponding to various intron and promoter sequences did not produce detectable interference

injection of dsRNA produces a pronounced decrease or elimination of the endogenous mRNA transcript

dsRNA-mediated interference showed a surprising ability to cross cellular boundaries

很快人们认识到RNAi发现的技术新颖
不是马上人人意识到新生物学
Richard W. Wagner and Lin Sun
News and Views in Nature
Functional genomics Double-stranded RNA poses puzzle
***Nature* 391, 744 - 745 (1998)**

On page 806 of this issue, Fire and colleagues describe a remarkable and surprising technique for inhibiting gene function in *C. elegans*.

Possible mechanism

Does dsRNA perform a biological function in *C. elegans* (and is this function titrated out by the microinjected dsRNA)? Does a similar phenomenon exist in other organisms? What would happen if transgenic animals or plants were generated expressing both the sense and antisense strands of a transgene?

机遇，有准备的头脑，还要有决心

C. Elegans:

long RNAs effective (can be easily converted into the functionally active 20mers in worms）

diffusion （of siRNAs in worms)

Ignored initially by Fire after 1991 till 1998

and not followed by Guo and Kemphues after 1995

Guo and Kemphues

什么做的好

为什么错失良机

科学研究的诚实
integrity in science

科学常规是相信科学家和科学工作者
没有真实的资料和数据，科学无法进展

造假是不被容忍的，
在国际科学界：基本没有第二次机会

造假是愚蠢的

重要的假，总会被发现
不重要的，不过是欺骗自己

失去了：
他人的根本信任
和自我尊重

一时没有好论文，以后还有可能
一次论文造假，永无获得大家原谅的可能（虽然有个别人原谅的可能）
一辈子没有好论文，无造假是好人
一辈子有一篇假论文，人格非得减低

相关的是说谎话
有许多类似点

资料数据和自己预计不同怎么办？
影响发论文怎么办？

有些重要发现就在这里面！

RNA interference (RNAi)

Guo, S. & Kemphues, K. J. *par-1*, a gene required for establishing polarity in *C. elegans* embryos, encodes a putative Ser/Thr kinase that is asymmetrically distributed. *Cell* **81**, 611-620 (1995).

Fire, A. *et al*. Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* **391**, 806-811 (1998).

Cornell大学华裔研究生郭苏和RNAi

在研究*C. elegans* 里面一个基因*par-1*功能过程中，Guo用反意（antisense）RNA方法来看其功能，发现它有表型，一般来说这就证明*par-1有功能*。但她用有意（sense）来作对照时，结果它也有表型，这样， antisense的结果就不能用来说明*par-1*的功能。
从发表论文来看，这样的结果没有帮助，而且会引起审稿者疑问，她们用基因突变来证明*par-1的功能，而RNA这些对论文被接受没有帮助。*
从长远看，当时不能断定这样的发现有意义，可能是*par-1*特别，或*C. elegans*特别

她们发表了这些结果：诚实的发现

Guo, S. & Kemphues, K. J. *par-1*, a gene required for establishing polarity in *C. elegans* embryos, encodes a putative Ser/Thr kinase that is asymmetrically distributed. *Cell* 81, 611-620 (1995).

影响了Fire et al

如果有谁自作聪明或看眼前理由
当时把不合一时理论的结果藏起来
不过是愚蠢的表现
即使是不谈科学，只看功利主义：
　　说个玩笑比喻，那也可能导致捡了一篇文章丢了诺贝尔

科学上，各人遇到重要突破的几率不是很高的

遇到不可解释和不方便的结果时，不应该轻易放弃

Tom Cech发现RNA有酶活性，也是偶然没有预期的多一条带

所以

资料和数据不真实也是

科学中**最愚蠢的行为**

中间还有一个小事：

毕业快重要还是更多发现重要？

Guo, S. & Kemphues, K. J. 没有继续研究她们自己在*Cell*, 1995发表的偶尔发现：

（下面做另外一个研究）
Guo S, Kemphues KJ.
A non-muscle myosin required for embryonic polarity in Caenorhabditis elegans. Nature. 1996 Aug 1;382(6590):455-8.

老师和学生的关系

老师：
要经常和学生讨论科学
要鼓励学生和其他老师学生讨论科学
经常看所有原始结果
要把好质量关
　　不能压学生只出“好”结果
　　看到“坏”结果时，不能迁怒于学生

学生：
要经常和老师，同学讨论科学
不要因噎废食（因怕别人竞争而不讨论）
找到自己的科学朋友：your support, your stimulation
要诚实给导师看原始结果
不要怕结果“难看”

例子：Watson, Crick, Brenner

合作者
同实验室：
和PI和其他直接合作者协商
公平和利益兼顾
其它实验室
事先商定，事后协商
考虑因素
主体
工作量
待人以诚
风物常以放眼量：
不要因争一篇文章失去合作，失去长远
正反两方面例子，历史和现状，中外

Perseverance 坚持不懈

二种不同类型的例子

一. 有时候要在别人轻视下，自己有信心、有决心、花时间认真做好的工作

Brenner （六、七十年代）

Nüsslein－Volhard and Wieschaus （七十年代）

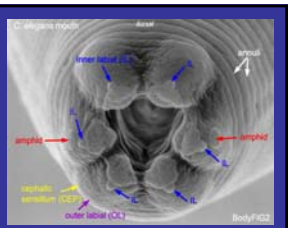
Mario R. Capecchi （八十年代）
Thomas, K.R. & Capecchi, M.R. *Cell* **51**, 503–512 (1987).
Mansour, S.L., Thomas, K.R. & Capecchi, M.R. *Nature* **336**, 348–352. (1988)

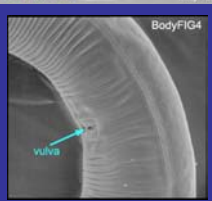
Prasher和GFP （九十年代）

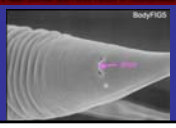
C. elegans

Before we talk about cell polarity in C. elegans, let's review a bit of the history of using worms in biology research

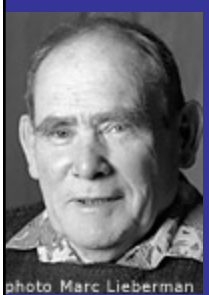
2002







Sydney Brenner



born January 13, 1927, South Africa

目前在美国伯克利分子科学研究所的Brenner，生于南非约翰内斯堡郊外的杰米斯顿Germiston。

父母是犹太移民，父亲20世纪初逃出东欧将被苏联占领的小国到伦敦后，没有足够的钱买去美国的船票，只好到南非。他父亲是皮革匠，家就安在皮革铺的后面，父亲一生不识字更不会写字，却通几种语言。

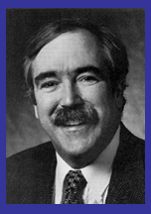
Brenner4岁以前，邻居裁缝的妻子用她家做桌布的报纸教布勒呐认字，是他的启蒙教育。大概4岁半时，父亲有个顾客Mrs. MacCartney见小Brenner读书，对老布勒呐说应该送这小孩读书，父亲说读不起。她把小Brenner收到自己管的幼儿园去。这是一个早期发现Brenner的才能而且帮助他的人， Brenner到七十多岁还记得她。

虽然比同班小三岁， Brenner在学校一直不错，不过从不是第一，大约前六名，据他说，小学中学名次比他前的同学长大后智力平庸。(went on to intellectual obscurity)

Brenner喜欢用图书馆，从小学起一生读了很多书和文章，穷的时候偷过一本喜欢的书。对科学的兴趣也来自课外书籍。

Brenner S (2001) My life in science. Science Archive Limited, London

1995



Edward B. Lewis | Christiane Nüsslein-Volhard | Eric F. Wieschaus

他们分别受不同的轻视， Nüsslein-Volhard更因为是女性而找工作不容易（即使在刚刚做出以后诺贝尔奖研究后）

Lewis from the 50s to the 70s

Nüsslein-Volhard and Wieschaus in the 70s at EMBO Lab in Heidelberg

Nüsslein-Volhard in the 70s at Tubingen and Max Planck Institute for Dev Biol

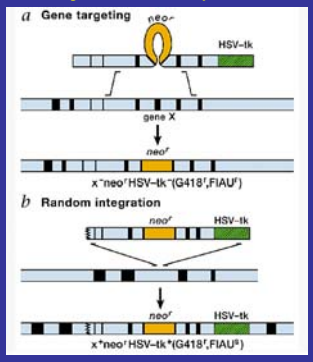
Mario R. Capecchi

智商低的人给智商高的人发奖，好像是世界上比较普遍的规律，从华盛顿、北京到斯德哥尔摩，好像都是这样的

对比那张发奖的照片，这张照片大概才比较接近他幸福的时刻

(b. 1937); B.S. 1961, Antioch College; Ph.D. 1967, Harvard University.

Mario R. Capecchi at University of Utah



The nucleoside analog FIAU specifically kills cells with functional *HSV-tk* genes, but is not toxic to cells with only cellular *Tk*.

G418, kills cells without a functional neomycin resistant gene

Thomas, K.R. & Capecchi, M.R. *Cell* **51**, 503-512 (1987).

Mansour, S.L., Thomas, K.R. & Capecchi, M.R. *Nature* **336**, 348-352. (1988)

Mario R. Capecchi & Perseverance

因为母亲反对法西斯被捕入狱，他四岁多到九岁期间，在战乱的意大利做流浪街头的孤儿

当他提出基因剔除技术时，NIH六年没有给他资助

Lack of NIH support for his knockout (literarily and metaphorically) work

Prasher和GFP

the hydromedusa Aequorea victoria

Prasher et al., 1986, Biochem. Biophys. Res. Comm. 126, 1259-1268

Prasher DC, McCann RO, Longiaru M, Cormier MJ. Sequence comparisons of complementary DNAs encoding aequorin isotypes.
Biochemistry. 1987 Mar 10;26(5):1326-32.

Prasher DC, Eckenrode VK, Ward WW, Prendergast FG, Cormier MJ.
Woods Hole Oceanographic Institution, Biology Department, MA 02543.
Primary structure of the Aequorea victoria green-fluorescent protein.
Gene. 1992 Feb 15;111(2):229-33.

Chalfie M, Tu Y, Euskirchen G, Ward WW, Prasher DC.
Green fluorescent protein as a marker for gene expression.
Science. 1994 Feb 11;263(5148):802-5.
A complementary DNA for the Aequorea victoria green fluorescent protein (GFP) produces a fluorescent product when expressed in prokaryotic (Escherichia coli) or eukaryotic (Caenorhabditis elegans) cells. Because exogenous substrates and cofactors are not required for this fluorescence, GFP expression can be used to monitor gene expression and protein localization in living organisms.

Heim R, Prasher DC, Tsien RY. Wavelength mutations and posttranslational autoxidation of green fluorescent protein.
Proc Natl Acad Sci U S A. 1994 Dec 20;91(26):12501-4.

Prasher和high impact papers (few)

1. Haseloff J, Siemering KR, Prasher DC, Hodge S.Removal of a cryptic intron and subcellular localization of green fluorescent protein are required to mark transgenic Arabidopsis plants brightly. Proc Natl Acad Sci U S A. 1997 Mar 18;94(6):2122-7.
2. Prasher DC. Using GFP to see the light. Trends Genet. 1995 Aug;11(8):320-3. Review.
3. Heim R, Prasher DC, Tsien RY.Wavelength mutations and posttranslational autoxidation of green fluorescent protein. Proc Natl Acad Sci U S A. 1994 Dec 20;91(26):12501-4
4. Chalfie M, Tu Y, Euskirchen G, Ward WW, Prasher DC.Green fluorescent protein as a marker for gene expression. Science. 1994 Feb 11; 263(5148):802-5.
5. Cody CW, Prasher DC, Westler WM, Prendergast FG, Ward WW. Chemical structure of the hexapeptide chromophore of the Aequorea green-fluorescent protein. Biochemistry. 1993 Feb 9;32(5):1212-8.
6. Hanniek LI, Prasher DC, Schultz LW, Deschamps JR, Ward KB.Preparation and initial characterization of crystals of the photoprotein aequorin from Aequorea victoria. Proteins. 1993 Jan;15(1):103-7.
7. Prasher DC, Eckenrode VK, Ward WW, Prendergast FG, Cormier MJ. Primary structure of the Aequorea victoria green-fluorescent protein. Gene. 1992 Feb 15;111(2):229-33.

8. O'Kane DJ, Prasher DC.Evolutionary origins of bacterial bioluminescence. Mol Microbiol. 1992 Feb;6(4):443-9. Review.
9. O'Kane DJ, Woodward B, Lee J, Prasher DC.Borrowed proteins in bacterial bioluminescence. Proc Natl Acad Sci U S A. 1991 Feb 15;88(4):1100-4.
10. Prasher DC, O'Kane D, Lee J, Woodward B.The lumazine protein gene in Photobacterium phosphoreum is linked to the lux operon. Nucleic Acids Res. 1990 Nov 11;18(21):6450.
11. Cormier MJ, Prasher DC, Longiaru M, McCann RO. The enzymology and molecular biology of the Ca2+-activated photoprotein, aequorin. Photochem Photobiol. 1989 Apr;49(4):509-12.
12. Phillips GJ, Prasher DC, Kushner SR.Physical and biochemical characterization of cloned sbcB and xonA mutations from Escherichia coli K-12. J Bacteriol. 1988 May;170(5):2089-94.
13. Prasher DC, McCann RO, Longiaru M, Cormier MJ.Sequence comparisons of complementary DNAs encoding aequorin isotypes. Biochemistry. 1987 Mar 10;26(5):1326-32.
14. Prasher DC, Conarro L, Kushner SR. Amplification and purification of exonuclease I from Escherichia coli K12. J Biol Chem. 1983 May 25;258(10):6340-3.
15. Prasher DC, Carr MC, Ives DH, Tsai TC, Frey PA. Nucleoside phosphotransferase from barley. Characterization and evidence for ping pong kinetics involving phosphoryl enzyme. J Biol Chem. 1982 May 10;257(9):4931-9.
16. Richard JP, Prasher DC, Ives DH, Frey PA. Chiral [18O]phosphorothioates. The stereochemical course of thiophosphoryl group transfer catalyzed by nucleoside phosphotransferase. J Biol Chem. 1979 Jun 10;254(11):4339-41.

他不仅没有多少“大杂志”文章，
连研究经费和实验室都保不住

1992: when he cloned and sequenced the GFP cDNA
Prasher was at
Biology Department,
Woods Hole Oceanographic Institution, MA 02543.

1994: when Chalfie and Tsien successfully used his cDNA
Prasher was at
Animal and Plant Health Service,
U.S. Department of Agriculture,
Otis Plant Protection Center, Building 1398,
Air Force National Guard Base, Otis, MA 02542-5008

他仍给科学留下重要贡献：坚持研究和发现GFP

文章质量和杂志

最近几年中国也跟世界接轨了认定科学研究的结果要尽量发表到好杂志（读者多的杂志）去，不过国际上如何发文章不同科学家也有不同意见，我以为：

好的研究，发到好的杂志，对作者有帮助
杰出研究，发到哪里，不是特别重要
差的研究，发到好杂志，是在专家同行面前出洋相
例子
错的研究，发到好杂志，比出洋相还糟糕

不好的研究为了发文章，即使上了好杂志，花费的时间也不值得。如果认为这样的人聪明，是小聪明
真聪明，就不要浪费这样的时间，不聪明上了，专家也不会尊重，只会得到不懂行、不仔细的人尊重
什么尊重对你重要？

有时候

在本领域受挫折后，改正错误（不是造假性质的，是有道理的诚实错误honest mistakes），

还要有勇敢面对错误，

继续坚持研究

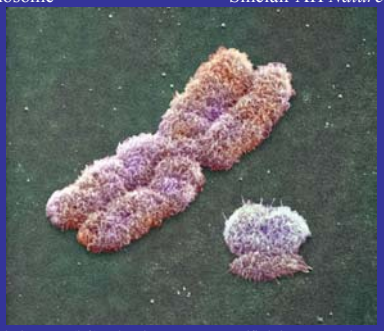
David C. Page
坚持研究男子汉的分子生物学：
从单基因到Y染色体
从失误到成功

Whitehead Institute and MIT

Persistence: the hunt for molecular basis of the man

Question: What makes a man a man?

Y chromosome Sinclair AH *Nature* 1959



Male make-up. The human X (left) and Y chromosomes, magnified about 10,000 times.
Willard HF (2003) Tales of the Y chromosome. *Nature* 423:810-3

决定“男性”的基因

Y chromosome — Sinclair AH *Nature* 1959
H-Y antigen histocompatibility SS — Wachtel et al *Nature* 1975
Not H-Y — McLaren A et al *Nature* 1984
TDF interval 1 region — Page DC et al. *CSHSQB* 1986
ZFY — Page DC et al. Cell 1987

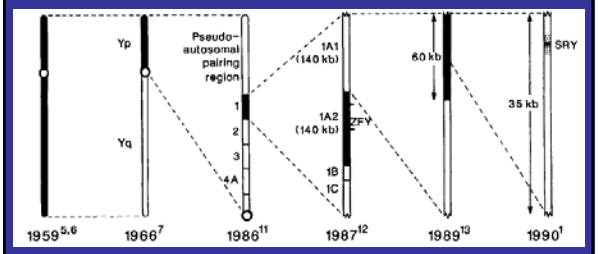
McLaren A. (1990) *Nature* 346:216-7.

Page DC, Mosher R, Simpson EM, Fisher EM, Mardon G, Pollack J, McGillivray B, de la Chapelle A, Brown LG (1987)
The sex determining region of the human Y chromosome encodes a finger protein.
Cell 51:1091-104.

a 230-kilobase segment of the human Y chromosome
The cloned region spans the deletion in a female who carries all but 160 kilobases of the Y.
Certain DNA sequences within this region were highly conserved during evolution; homologs occur on the Y chromosomes of all mammals examined. In particular, homologous sequences are found within the sex-determining region of the mouse Y chromosome.
The nucleotide sequence of this conserved DNA on the human Y chromosome suggests that it encodes a protein with multiple "finger" domains.
Very similar DNA sequences occur on the X chromosome of humans and other mammals. We discuss the possibility that the Y-encoded finger protein is the testis-determining factor, and propose models of sex determination accommodating the finding of a related locus on the X chromosome. The presence of similar sequences in birds suggests a possible role not only in the XX/XY sex determination system of mammals, but also in the ZZ/ZW system of birds.

Page DC. (1988) Is ZFY the sex-determining gene on the human Y chromosome?
Philos Trans R Soc Lond B Biol Sci. 1988 322:155-7.

Sinclair AH, Foster JW, Spencer JA, Page DC, Palmer M, Goodfellow PN, Graves JA (1988) Sequences homologous to ZFY, a candidate human sex-determining gene, are autosomal in marsupials.
Nature 336:780-3.
Either the genetic pathways of sex determination in marsupials and eutherians differ, or they are identical and ZFY is not the primary signal in human sex determination.
Mardon G, Mosher R, Disteche CM, Nishioka Y, McLaren A, Page DC.
Duplication, deletion, and polymorphism in the sex-determining region of the mouse Y chromosome.Science. 1989 243:78-80.
Mardon G, Page DC.The sex-determining region of the mouse Y chromosome encodes a protein with a highly acidic domain and 13 zinc fingers.
Cell. 1989 56:765-70.
Schneider-Gadicke A, Beer-Romero P, Brown LG, Nussbaum R, Page DC Human ZFX escapes X inactivation. Cell. 1989 57:1247-58.



McLaren A. (1990) *Nature* 346:216-7.

the X,t(Y;22) female has a deletion of a second portion of interval 1A--a portion corresponding closely to that present in the XX intersexes. This resolves the apparent contradiction. Nonetheless, phenotype-genotype correlations suggest that two or more genetic elements in interval 1A may contribute to the sex-determining function of the Y chromosome. The X,t(Y;22) female lacks the ZFY gene but does not exhibit the complex phenotype known as Turner's syndrome, arguing against the hypothesis that ZFY is the Turner's syndrome gene on the Y chromosome

Page DC, Fisher EM, McGillivray B, Brown LG. (1990) *Nature* 346:279-81

SRY (for sex determining region Y)
the elusive testis determining gene, TDF

Sinclair AH, Berta P, Palmer MS, Hawkins JR, Griffiths BL, Smith MJ, Foster JW, Frischauf AM, Lovell-Badge R, Goodfellow PN (1990)
A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif.
Nature 346:240-4.
Gubbay J, Collignon J, Koopman P, Capel B, Economou A, Munsterberg A, Vivian N, Goodfellow P, Lovell-Badge R. (1990).
A gene mapping to the sex-determining region of the mouse Y chromosome is a member of a novel family of embryonically expressed genes.
Nature 346:245-50.
Page DC, Fisher EM, McGillivray B, Brown LG. (1990)
Additional deletion in sex-determining region of human Y chromosome resolves paradox of X,t(Y;22) female
Nature 346:279-81

David Page moved onto the physical and sequencing of the human Y chromosome

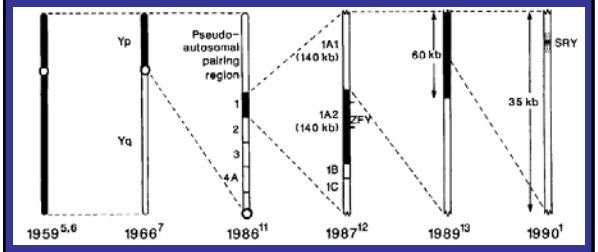
Foote S, Vollrath D, Hilton A, Page DC.
The human Y chromosome: overlapping DNA clones spanning the euchromatic region.
Science. 1992 Oct 2;258(5079):60-6.

Vollrath D, Foote S, Hilton A, Brown LG, Beer-Romero P, Bogan JS, Page DC.
The human Y chromosome: a 43-interval map based on naturally occurring deletions.
Science. 1992 Oct 2;258(5079):52-9.

Tilford CA, Kuroda-Kawaguchi T, Skaletsky H, Rozen S, Brown LG, Rosenberg M, McPherson JD, Wylie K, Sekhon M, Kucaba TA, Waterston RH, Page DC.

A physical map of the human Y chromosome.
Nature. 2001 Feb 15;409(6822):943-5.

SRY是男子的决定性基因，ZFY不是



McLaren A. (1990) *Nature* 346:216-7.

很多有趣和重要的发现，人类基因组测序中结果最有趣的一个

The male-specific region of the Y chromosome, the MSY, differentiates the sexes and comprises 95% of the chromosome's length. Here, we report that the MSY is a mosaic of heterochromatic sequences and three classes of euchromatic sequences: X-transposed, X-degenerate and ampliconic. These classes contain all 156 known transcription units, which include 78 protein-coding genes that collectively encode 27 distinct proteins.
The X-transposed sequences exhibit 99% identity to the X chromosome. The X-degenerate sequences are remnants of ancient autosomes from which the modern X and Y chromosomes evolved. The ampliconic class includes large regions (about 30% of the MSY euchromatin) where sequence pairs show greater than 99.9% identity, which is maintained by frequent gene conversion (non-reciprocal transfer).

2003年6月19日

Skaletsky H, Kuroda Kawaguchi T, Minx PJ, Cordum HS, Hillier L, Brown LG, Repping S, Pyntikova T, Ali J, Bieri T, Chinwalla A, Delehaunty A, Delehaunty K, Du H, Fewell G, Fulton L, Fulton R, Graves T, Hou SF, Latrielle P, Leonard S, Mardis E, Maupin R, McPherson J, Miner T, Nash W, Nguyen C, Ozersky P, Pepin K, Rock S, Rohlfing T, Scott K, Schultz B, Strong C, Tin Wllam A, Yang SP, Waterston RH, Wilson RK, Rozen S, Page DC.
（2003）
The male specific region of the human Y chromosome is a mosaic of discrete sequence classes.

Nature， 423:825 37.

2003年6月19日

Rozen S, Skaletsky H, Marszalek JD, Minx PJ, Cordum HS, Waterston RH, Wilson RK, Page DC.

Abundant gene conversion between arms of palindromes in human and ape Y chromosomes.

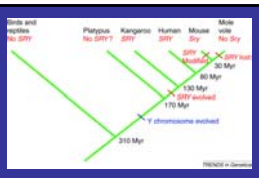
Nature， 423:873-6.

Eight palindromes comprise one-quarter of the euchromatic DNA of the male-specific region of the human Y chromosome, the MSY. They contain many testis-specific genes and typically exhibit 99.97% intra-palindromic (arm-to-arm) sequence identity. This high degree of identity could be interpreted as evidence that the palindromes arose through duplication events that occurred about 100,000 years ago. Using comparative sequencing in great apes, we demonstrate here that at least six of these MSY palindromes predate the divergence of the human and chimpanzee lineages, which occurred about 5 million years ago. The arms of these palindromes must have subsequently engaged in gene conversion, driving the paired arms to evolve in concert. Indeed, analysis of MSY palindrome sequence variation in existing human populations provides evidence of recurrent arm-to-arm gene conversion in our species. We conclude that during recent evolution, an average of approximately 600 nucleotides per newborn male have undergone Y-Y gene conversion, which has had an important role in the evolution of multi-copy testis gene families in the MSY

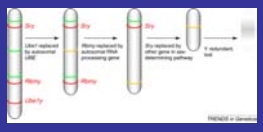
X–Y recombination became suppressed during evolution, an alternative mechanism had to emerge to maintain the sequence and function of the remaining Y-chromosome genes and to prevent the accumulation of inactivating mutations and the ultimate demise of the chromosome.

Rozen *et al*.: X–Y recombination has been replaced by extensive, ongoing recombination between the arms of the MSY palindromes — where the sequence on one arm of the palindrome alters or 'converts' the sequence on the other.

Willard HF (2003) Tales of the Y chromosome. Nature. 423:810-3.



Timescale of evolution of the mammalian Y chromosome and *SRY*.



The loss of the Y chromosome and the *Sry* gene in mole voles (genus *Ellobius*). The ancestral rodent Y (left) retained several genes that are crucial for male differentiation, such as *Sry*, *Rbmy* and *Ube1y* (red), as well as other genes that still complemented their X-borne partners (green). These were all lost (in arbitrary order), and their functions replaced by genes on autosomes or the X. Eventually, the entire Y became redundant and was lost (right).

10 Myr to go in humans

Marshall Graves, J. A. *Trends Genet.* **18**, 259–264 (2002).

David C. Page
Whitehead Institute and MIT

Old Technology in New Breakthroughs

Gurdon JB (1975) Attmepts to analyse the biochemical basis of regional differences in animal eggs**.** Ciba Found Symp (29):223-39.
Marbaix G et al. (1975). Proc Natl Acad Sci U S A. 1975 Aug;72(8):3065-7.
Chan L, Kohler PO, O'Malley BW. (1976) J Clin Invest. 57:576-85.

Expression Cloning

Julius D, MacDermott AB, Axel R, Jessell TM. (1988). Molecular characterization of a functional cDNA encoding the serotonin 1c receptor. Science 241:558-64.
Science 244:1057-62, 1989
Proc Natl Acad Sci 86:6793-7, 1989.
Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. Nature 374:542-6, 1995.
Julius D, Molecular biology of serotonin receptors. Annu Rev Neurosci. 1991;14:335-60.
An ionotropic ATP receptor Nature 371:519-23, 1994

Brake AJ, Julius D (1996) Signaling by extracellular nucleotides. Annu Rev Cell Dev Biol. 12:519-41.

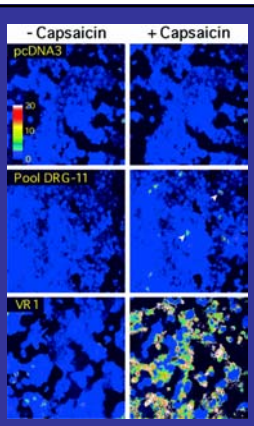
David Julius
UCSF

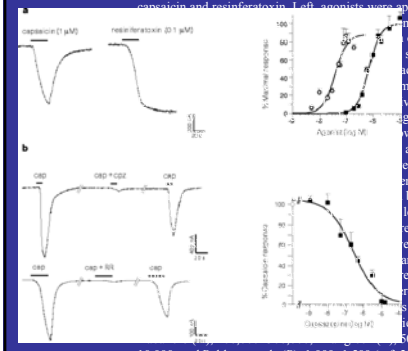
发现了辣味和痛觉的分子生物学机理

Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D (1997)

The capsaicin receptor: a heat activated ion channel in the pain pathway

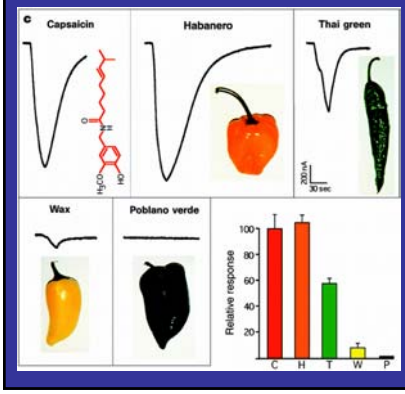
Nature 389:816-24.





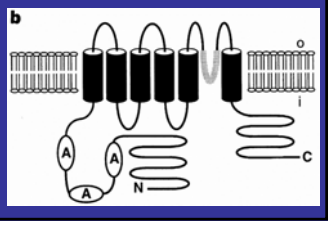
VR1 responds to purified vanilloids and pepper extracts. **a**, Activation of VR1 by capsaicin and resiniferatoxin. Left, agonists were applied sequentially to the same ...nts were recorded in the whole-cell ... of agonist application. Right, ... squares) and resiniferatoxin (open ...ach oxocyte to a response obtained ...maximal response to capsaicin. ...ve independent oocytes. The Hill ...gonism by capsazepine (cpz) and ...ws reversible block of capsaicin ... after 2 min pretreatment. Slash ...espectively (n = 3). A capsazepine ...endent oocytes for each point). ... by capsaicin alone in each oocyte. ... left shows reversible block of a ...red (RR; 10 M). Slash marks ...ely (n = 3). **c**, Responses to ...arieties of peppers in oocytes ...elative potencies of each pepper ...re normalized in each cell to ...s evoked no responses in water- ...ieties (in Scoville units) are: ...50,000–100,000; wax (W), 5,000–10,000; and Poblano verde (P), 1,000–1,500 (ref. 23). Capsaicin (C) is rated as 16 106 units.

VR1 responds to purified vanilloids and pepper extracts

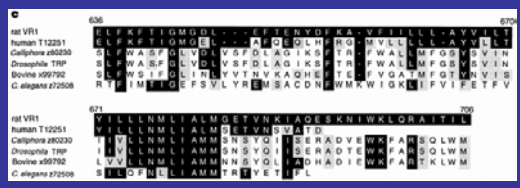


Activation of VR1 by capsaicin and resinferatoxin. Left, agonists were applied sequentially to the same *Xenopus* oocyte expressing VR1.

VR1 resembles store-operated channels



Similarities to *Drosophila* TRP



Alignment of VR1 with related sequences. Identical residues are in black boxes and conservative substitutions are in grey.

Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D
The cloned capsaicin receptor integrates multiple pain-producing stimuli.
Neuron 1998 Sep;21(3):531-43.

Caterina MJ, Rosen TA, Tominaga M, Brake AJ, Julius D. A capsaicin-receptor homologue with a high threshold for noxious heat
Nature 1999 Apr 1;398(6726):436-41.

VR1 is also activated by protons
VRL-1 does not respond to capsaicin, acid or moderate heat. VRL-1 is activated by high temperatures, a threshold ~ 52C

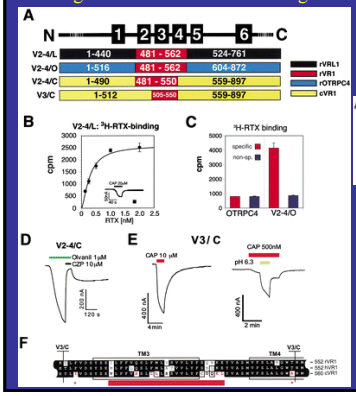
Montell, C. & Rubin, G. M. (1989). Molecular characterization of the *Drosophila trp* locus: A putative integral membrane protein required for phototransduction. *Neuron* 2:1313-1323.

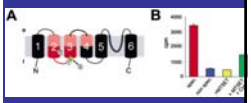
transient receptor potential (trp)

but the roles of the human homologs are still in the early stages of investigation

Cited from
Clapham DE (1996) *Neuron* 16:1069-72.
Four recent papers from Cell Press wrestle with the function of the Drosophila melanogaster (fruit fly) eye-specific *trp* gene…the conclusions clarify fly vision,
TRP is a Ca2+-permeant, light-activated, store-dependent channel with regulated cellular distribution and function

Vanilloid Sensitivity Is Transferred to VR1-Related Homologs through Exchange of Subdomains Containing Transmembrane Regions 2–4



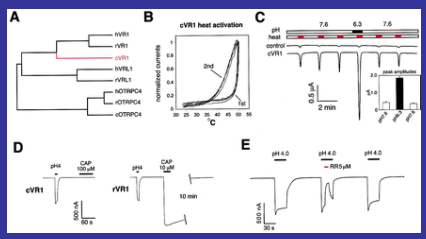


Accessibility of a Critical Residue from the Aqueous Phase

Predicted location of S512, substituted by cysteine in mutant S512C (yellow)

鸟类不怕辣、而哺乳类怕辣的分子基础

Jordt SE, Julius D (2002).
Molecular basis for species-specific sensitivity to "hot" chili peppers.
Cell 108:421-30



The Chicken VR1 Ortholog Responds to Noxious Heat or Protons, but Not to Capsaicin

痛觉的分子生物学专家

Caterina MJ, Julius D (2001) The vanilloid receptor: a molecular gateway to the pain pathway.
Annu Rev Neurosci 24:487-517

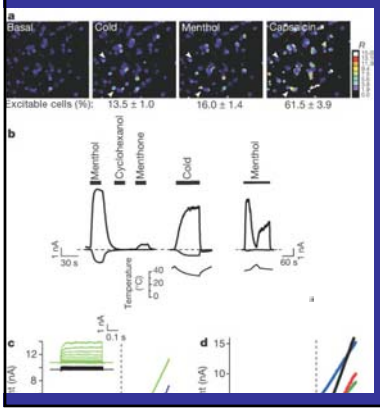
Julius D, Basbaum AI (2001). Molecular mechanisms of nociception.
Nature 413:203-10

Expression Cloning for Cold Receptors

Heat is the presence of things
Cold is the absence of things

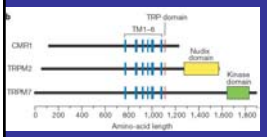
McKemy DD, Neuhausser WM, Julius D (2002)
Identification of a cold receptor reveals a general role for TRP channels in thermosensation.
Nature 416:52-8

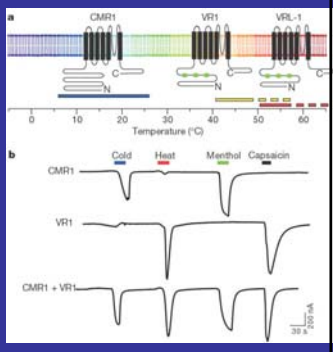
Responses of dissociated trigeminal neurons to cold , menthol



cold (7 ° C),
menthol (500 uM)
and capsaicin (1 uM)

CMR1 is a member of the TRP family of ion channels !





As few as three ion channels (CMR1, VR1 and VRL-1) may provide coverage for a remarkably wide range of temperatures (8–28, >43 and >50 ° C, respectively)

do not respond to all commonly experienced temperatures, such as ultra-cold (<8 ° C) or warm (30–40 ° C)

others

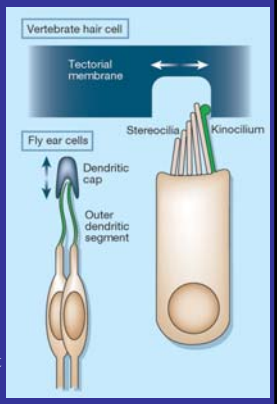
Xu et al., (2002) TRPV3 is a calcium-permeable temperature-sensitive cation channel. Nature 418:181-186
Jiang CH, Mazieres L, Lindstrom S
Cold- and menthol-sensitive C afferents of cat urinary bladder
J Physiology (London)
Story GM, Peier AM, Reeve AJ, et al. ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures
Cell 112 (6): 819-829 MAR 21 2003
Finger TE, Bottger B, Hansen A, et al. (2003)
Solitary chemoreceptor cells in the nasal cavity serve as sentinels of respiration
PNAS 100: 8981-8986

听、触等

压力感觉的分子生物学

Strassmaier M, Gillespie PG (2002).
Curr Opin Neurobiol 12 : 380-386

The elusive transduction channel is the key player in mechanical transduction by the sensory hair cells of the inner ear. Multiple factors have thwarted molecular identification of this channel, including the lack of a definitive pharmacological signature, the paucity of hair cells, and the uniqueness of their transduction mechanism, At present, we are forced to speculate as to the transduction channel's identity; functional characteristics suggest, however, that it may well belong to transient receptor potential superfamily of ion channels



Corey DP.
New TRP channels in hearing and mechanosensation
Neuron. 2003 Aug 14;39(4):585-8.

The idea of a mechanically gated ion channel
1950s and 60s by Lowenstein on Pacinian corpuscles, by Ottoson and Shepherd on muscle spindles, and by Davis on cochlea
The first cloned channel shown to be directly activated by membrane tension was the MscL channel of bacteria (Sukharev et al., Nature *368*, 265-268,1994), but it has no homolog in eukaryotes

The first TRP channel implicated in mechanosensation (mutatants defective in osmotic avoidance and touch nose): the *C. elegans* OSM-9 (Colbert, H.A., Smith, T.L., and Bargmann, C.I. (1997). J. Neurosci. *17*, 8259-8269)
the vertebrate TRPV4 channel is mechanosensitive (Strotmann et al., Nat. Cell Biol 2000, Liedtke et al., Cell 2000, Wissenbach et al., FEBS Lett 2000 ; Delany et al., Physiol. Genomics 2001

Walker, R.G., Willingham, A.T., and Zuker, C.S. (2000). A Drosophila mechanosensory transduction channel *Science 287, 2229-2234 (*NOMPC)

Kim J, Chung YD, Park DY, Choi S, Shin DW, Soh H, Lee HW, Son W, Yim J, Park CS, Kernan MJ, Kim C (2003).
Department of Genetics, Hanwha Chemical Co. R&D Center, Sinsung-Dong, Yusung-Gu, Daejeon 305-345, Korea.

A TRPV family ion channel required for hearing in Drosophila
Nature *424*, 81-84

Sidi, S., Friedrich, R., and Nicolson, T. (2003). NompC TRP channel required for vertebrate sensory hair cell mechanotransduction Science *301*, 96-99

How Close Are We to Understand Human Hearing Now?

Di Palma, F., Belyantseva, I.A., Kim, H.J., Vogt, T.F., Kachar, B., and Noben-Trauth, K. (2002). Mutations in Mcoln3 associated with deafness and pigmentation defects in varitint-waddler (Va) mice.

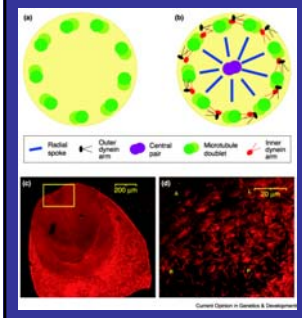
Proc. Natl. Acad. Sci. USA *99*, 14613-14615

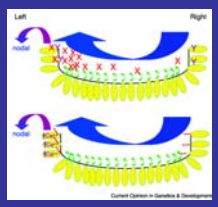
Deafness in spontaneously occurring mouse mutants

positional cloning: Mcoln3 as the gene mutated in varitint-waddler

Mcoln3 encodes a TRP member.

Structure and distribution of node monocilia.





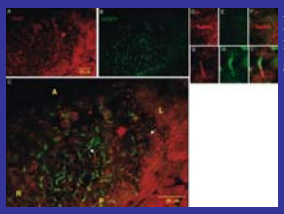
McGrath J, Brueckner M. (2003) Cilia are at the heart of vertebrate left-right asymmetry. Curr Opin Genet Dev. 13:385-92

TRP: More Surprises

Polycystic kidney disease in humans are caused by mutations in PKD1 and PKD2 genes（多发行肾囊肿的患病机理）

When expressed in CHO cells together, PKD1 and PKD2 form a Ca2+-permeable ion channel (Hanaoka, et al., Nature *408*, 990-994, 2000)

Left-Right Asymmetry （左右不对称的机理）
P. Pennekamp, C. Karcher, A. Fischer, A. Schweickert, B. Skryabin, J. Horst, M. Blum and B. Dworniczak, The ion channel polycystin-2 is required for left-right axis determination in mice. *Curr Biol* **12** (2002), pp. 938–943

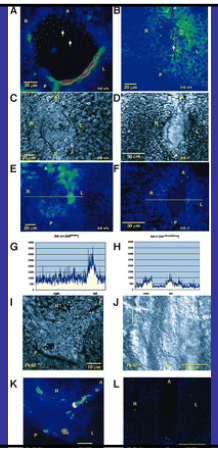


polycystin-2 is found in all node monocilia without any LR asymmetry in e7.75 mouse embryo

GFP-left-right dynein
At e7.75–e8.0

central monocilia containing both polycystin-2 and lrd, and peripheral cilia containing exclusively polycystin-2

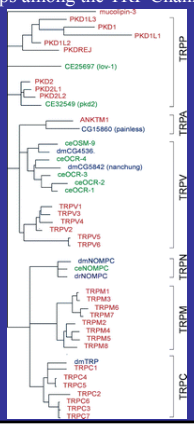
McGrath J, Somlo S, Makova S, Tian X, Brueckner M Two populations of node monocilia initiate left-right asymmetry in the mouse. Cell. 2003 Jul 11;114(1):61-73.



Calcium Signaling at the Node of e7.75 Mouse Embryos

Basora N, Boulay G, Bilodeau L, Rousseau E, Payet MD. 20-hydroxyeicosatetraenoic acid (20-HETE) activates mouse TRPC6 channels expressed in HEK293 cells J Biol Chem. 2003 Aug 22;278(34):31709-16.
Watanabe H, Vriens J, Prenen J, Droogmans G, Voets T, Nilius B. Anandamide and arachidonic acid use epoxyeicosatrienoic acids to activate TRPV4 channels.
Nature. 2003 Jul 24;424(6947):434-8
Greka A, Navarro B, Oancea E, Duggan A, Clapham DE TRPC5 is a regulator of hippocampal neurite length and growth cone morphology.
Nat Neurosci. 2003 Aug;6(8):837-45
New target molecules in the drug control of blood pressure and circulation.
Curr Drug Targets Cardiovasc Haematol Disord. 2003 Mar;3(1):59-72
TRP) channels as potential drug targets in respiratory disease.
Cell Calcium. 2003 May-Jun;33(5-6):551-8
Role and regulation of TRP channels in neutrophil granulocytes.
Cell Calcium. 2003 May-Jun;33(5-6):533-40.

Phylogenetic Relationships among the TRP Channel Superfamily



很快和以后，如果你碰到有些“有经验的人”、认为“懂了”科学后表示对研究的厌烦和悲观

激动人心的日子已经过去？
对当代研究不感到兴奋？

分子生物学：就是克隆DNA，纯化蛋白质？
神经生物学：就是针头在这里刺一下那里刺一下？

只要你感兴趣，你就不必给这样的思潮给吓倒了，激动人心的研究就发生在现在

外激素pheromones

They are a distinct and still poorly identified class of species- and gender- specific chemical cues that provide information about social and sexual status

They marked changes in animal behaviour and endocrine status.

They exist in most species, from single-cell organisms to mammals (but not clear in humans)

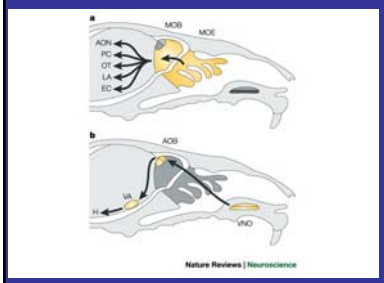
pheromones

in insects, pheromone-elicited behaviours include territory marking, colony identification, social hierarchy, reproductive status and mating rituals,

非常敏感: glypure and bombykol, the sex pheromones of the gypsy and silkworm moths, respectively, elicit responses in the male antenna at concentrations of only a few hundred molecules per square centimetre. It has been estimated that the amount of compound that is present in one female moth 一个母蛾外性激素could theoretically attract a billion male moths 十亿个公蛾(rodents: detection threshold for putative pheromone is remarkably low, near 10-11 M)

两类外激素信号 — those inducing immediate or 'releaser' effects (for example, aggression or mating behaviours) and those eliciting long-lasting or 'primer' effects, such as physiological and hormonal changes

Functional and anatomical segregation of the two mammalian olfactory systems.

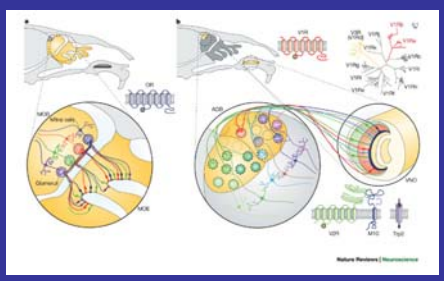


main olfactory epithelium (MOE)
main olfactory bulb (MOB)
anterior olfactory nucleus (AON), the piriform cortex (PC), the olfactory tubercle (OT), the entorhinal cortex (EC) and the lateral part of the cortical amygdala (LA)

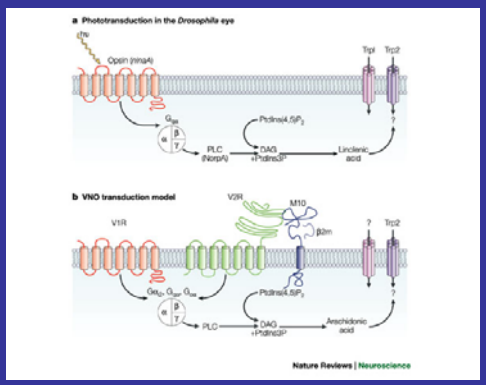
vomeronasal organ (VNO), accessory olfactory bulb (AOB)
vomeronasal amygdala (VA)
hypothalamus (H)

Catherine Dulac, A. Thomas Torello Sensory systems: Molecular detection of pheromone signals in mammals: from genes to behaviour. *Nature Reviews Neuroscience* 4, 551 - 562 (2003)

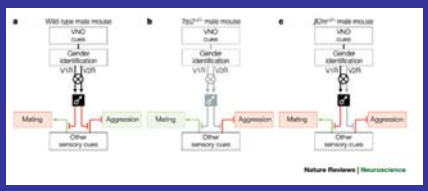
Cellular logic of sensory processing in the main and accessory olfactory systems.



A model of sensory transduction in vomeronasal neurons

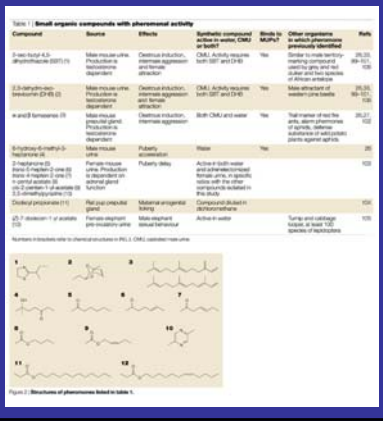


Role of the mouse vomeronasal organ (VNO) in gender discriminatio



Behavioural analysis of *Trp2-/-* males indicates that non-VNO-related sensory inputs, such as olfactory, auditory, tactile or visual cues, trigger mating behaviour (green) irrespective of the gender of the encountered mouse. So, in the absence of VNO activity, mating is the default behaviour of the male with a conspecific, and aggressive responses are suppressed (red).
Behavioural analysis of 2m-/- male mice indicates that V2R signalling is involved in the regulation of aggressive responses, but does not affect gender-specific reproductive responses. In the absence of V2R activity, appropriate gender-specific reproductive behaviours remain intact — male–male mating is inhibited and aggressive responses are suppressed.

Small organic compounds with pheromonal activity



the identity of the mammalian pheromones is poorly understood

proteinaceous components of complex secretions, such as urine and vaginal secretions
major urinary proteins
hamster vaginal secretion has a potent male attractant, aphrodisin, a molecule that elicits copulatory behaviours in male hamsters
lipocalin family of proteins

Catherine Dulac, A. Thomas Torello Sensory systems: Molecular detection of pheromone signals in mammals: from genes to behaviour. *Nature Reviews Neuroscience* 4, 551-562 (July, 2003)

Schaal B*†, Coureaud G*†, Langlois D†‡, Ginies C‡, Semon E‡ & Perrier G §
*** Centre Européen des Sciences du Goût, CNRS (fre 2328), 21000 Dijon, France**
‡ Unité Mixte de Recherche sur les Arômes, Inra, 21000 Dijon, France
§ Établissement National d'Enseignement Supérieur Agricole, 21000 Dijon, France
† These authors contributed equally to this work

Chemical and behavioural characterization of the rabbit mammary pheromone

Nature **424**, 68- 72 (03 Jul 2003)

the rabbit, *Oryctolagus cuniculus*

The mother nurtures her litter for 4–5 min once a day during the 2 weeks after birth

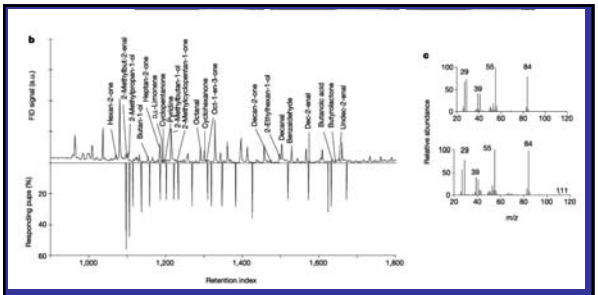
the pups need a reliable sensory tether for the rapid location of nipples, and competent behaviour to obtain milk successfully in a context of harsh competition between littermates.
keen chemosensory and tactile abilities linked with a typical head-searching pattern that ends in the grasping of a nipple within 3–5 s

The gas chromatography–olfaction (GCO) assay

The volatiles in milk were extracted, trapped and then desorbed into a gas chromatograph (GC) equipped with a sniffing device, permitting concurrent detection by neonatal rabbits and the flame ionization detector (FID).

pups responded either by short-range searching motions of the head directed to the sniff-port, or by attempts to seize it orally

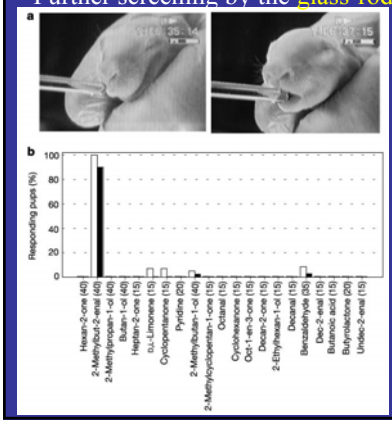
Sequence (duration 5 s) of a 2-day-old pup's searching–grasping response directed to the glass funnel of the GC sniff-port.



b, Typical chromatogram of rabbit milk effluvium (upper panel) and concurrent percentage of pups responding with searching–grasping responses (lower panel; inverted scale). The regions of the chromatogram eliciting more than 20% of responses (summed across 25 GCO runs) and the compounds eluting in these regions are shown. **c**, Mass spectra of 2MB2 of commercial origin (upper panel) and from rabbit milk (lower panel). Both scans were made at a retention index value of 1,096

21 compounds identified from GCO

Further screening by the glass-rod assay of milk vola



a, A 2-day-old pup at rest (left) and exhibiting grasping (right) to a glass rod carrying 2MB2.

b, Frequency of searching (open bars) and seizing (solid bars) directed to the glass rod carrying one of the 21 compounds identified in milk. Numbers in parentheses indicate the numbers of pups tested.

2-methylbut-2-enal (2MB): a single compound as the rabbit mammary pheromone

1) concentration-dependent: 10 ng/ml and 1 µg/ml
2) 60 min at ambient temperature, rabbit milk loses its effectiveness to evoke pup responsiveness: a decrease in 2MB2 concentration
3) activity reinstated by the addition of 2MB2
4) species-level generality and specificity of 2MB2 perception
generality of 2MB2 secretion and release in *Oryctolagus* females
effective on other closely related rabbits, but not on distant animals
colostrum and/or milk from rats, sheep, cows, horses and humans: no 2MB, no effect on rabbits
5) no learning or prenatal exposure required
6) present in milk irrespective of the female's diet, suggesting that it is produced *de novo* in the mammary tract

five criteria for pheromones

chemical simplicity

induction of an invariant behavioural response,

exclusive selectivity of stimulus

species specificity

no need for learning

The report will be viewed as a benchmark study in behavioural ecology and neuroscience. The authors combined expertise in investigation of the chemical senses, and in developmental psychobiology and analytical chemistry

Identification of a pheromone that induces suckling in newborn rabbits sets a standard for studies on other mammals, and should prime investigations of the neurobiological basis of this behaviour

Elliott M. Blass: Reproductive biology: Mammary messages *Nature* 424, 25–26 (2003)

Are there important questions for you?

Yes!

Do humans have a functional vomeronasal system?

Is human behaviour or reproductive physiology affected by pheromones, and if so, are those responses mediated by a vomeronasal system?
Yes
- pheromones and synchronization of the menstrual cycles of women
- compounds that purportedly elicit mood changes
- compounds thought to be pheromones might activate human vomeronasal receptor neurons and elicit stereotyped physiological responses
- VNO present in embryos, some adults

No
- Cells in VNO have not been shown to possess axons that connect to the brain
- AOB absent in the Old World monkeys, apes, and humans
- most of the human orthologues of rodent pheromone receptor genes seem to be non-functional pseudogene
- Human TRP2 is a pseudogene

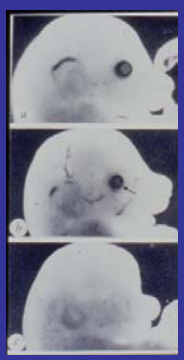
Pursue or not? the risk

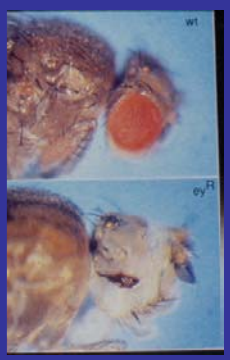
a hypothesis:
pheromone signalling might have been replaced by other sensory modalities — in particular colour vision, which emerged at a similar evolutionary time

Liman, E. R. & Innan, H. Relaxed selective pressure on an essential component of pheromone transduction in primate evolution. *Proc. Natl Acad. Sci. USA* **100**, 3328 3332 (2003).

再举一例

多彩多姿的眼睛





PAX-6基因和老鼠，果蝇的眼睛发育

异位表达PAX-6基因在果蝇引起异位眼睛形成

W. Gehring

腿上长眼睛

翅膀上长眼睛

W. Gehring

离开95年这么多年了，

除了果蝇的眼睛，

其他动物的任何器官，

还不能这样造出来

Only work on animals?

How about plants?

Cryptochromes

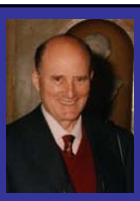
Enabling Plants and Animals to Determine Circadian Time

Anthony R. Cashmore

Cell, Vol 114, 537-543,

5 September 2003

Seymour Benzer



Born: October 15, 1921, New York City
Present Position: James Griffin Boswell Professor of Neuroscience California Institute of Technology, Pasadena, California 91125
Positions Held:
1967-present Division of Biology, California Institute of Technology: Professor of Biology, 1967-75; James Griffin Boswell Professor of Neuroscience, 1975-present
1953-1967 Biology Department, Purdue University: Associate Professor, 1953-1958; Professor, 1958-61; Stuart Distinguished Professor of Biophysics, 1961-67
1945-1953 Physics Department, Purdue University: Instructor, 1945-47; Assistant Professor, 1947-53

Publications

I. PHYSICS PERIOD (1-19)

Benzer, S. The high voltage germanium rectifier. *Experimental, NDRC Divison 14 Report #342*, November 1, 1944.

Benzer, S. High voltage and photosensitive characteristics in germanium. *Physical Review* 69, 683 (1946).

II. MOLECULAR BIOLOGY PERIOD (20-48)

Benzer, S. Fine structure of a genetic region in bacteriophage. *Proc. Natl. Acad. Sci. USA* 41, 344-354 (1955).

Benzer, S. On the topology of the genetic fine structure. *Proc. Natl. Acad. Sci. USA* 45, 1607-1620 (1959).

Benzer, S. On the topography of the genetic fine structure. *Proc. Natl. Acad. Sci. USA* 47, 403-415 (1961).

Benzer, S. and Champe, S. P. Ambivalent rII mutants of phage T4. *Proc. Natl. Acad. Sci. USA* 47, 1025-1038 (1961).

If one gets bored after one breakthrough

Look at some interesting scientists who continue to do creative research over a long career

如果怕生活变的重复：科学研究是可以不断有挑战的

III. BEHAVIORAL BIOLOGY PERIOD (49-116)

Benzer, S. Behavioral mutants of *Drosophila* isolated by countercurrent distribution. *Proc. Natl. Acad. Sci. USA* 58, 1112-1119 (1967).

Hotta, Y. and Benzer, S. Genetic dissection of the *Drosophila* nervous system by means of mosaics. *Proc. Natl. Acad. Sci. USA* 67, 1156-1163 (1970).

Konopka, R. J. and Benzer, S. Clock mutants of *Drosophila melanogaster. Proc. Natl. Acad. Sci. USA* 68, 2112-2116 (1971).

Hotta, Y. and Benzer, S. Mapping of behavior in *Drosophila* mosaics. *Nature* 240, 527-535 (1972).

Quinn, William G., Harris, W. A. and Benzer, S. Conditioned behavior in *Drosophila melanogaster. Proc. Natl. Acad. Sci. USA* 71, 708-712 (1974).

Dudai, Y., Jan, Y.-N., Byers, D., Quinn, W. G. and Benzer, S. *dunce*, a mutant of *Drosophila* deficient in learning. *Proc. Natl. Acad. Sci. USA* 73, 1684-1688 (1976).

Ready, D. F., Hanson, T. F. and Benzer, S. Development of the *Drosophila* retina, a neurocrystalline lattice. *Devel. Biol.* 53, 217-240 (1976).

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从这些故事里面，你可以得到什么?
(我希望)

你是否真喜欢生命科学研究
你是否愿意长期坚持
你发现自己需要怎么准备什么
你愿意不愿意努力
这里给你他人的经历，你自己得看能得到哪些有帮助的那些有害的

you get exposed to the experiences of others and you pick what you think are helpful or detrimental

hopefully, these stories will contribute in a small way to the foundation that stimulate you to come up with a way to make fundamental discoveries (some day)

后面有几个故事顺便讲了

多种感觉的分子生物学

做你自己

发现你自己的兴趣I
你自己的才能T (但愿 你的 I 和 T 匹配)

建立你自己的背景

你自己决定做什么

你的兴趣/才能/决心/（还可能有运气）的总和是一个特殊甚至独一无二组合，有助于你做出原创性original、创造性creatiive、重要的significant（甚至根本的fundamental）贡献

上路前的第一个临行赠言

贡献不能保证成功社会认可

一个科学家，只要工作杰出，对人类有贡献，
其它社会认可是次要的

比如：物理化学家 Nernst，长期被一人阻碍得奖
研究贡献高于或近于诺贝尔奖得主平均水平但没有得的：
分子生物学家 M. Meselson and F. Stahl，
重组DNA技术发明者H. Boyer and S. Cohen
发育神经生物学家Victor Hamburger等

一个科学家，虽然有办法使自己被称为著名科学家
或者得诺贝尔奖，
如果任何时候发现其科学贡献实质有限或有疑问
其基础削弱或不存在，其人格受疑问
例如：

中国同样

是否院士和是否作出过优秀科学：那个重要？

懂行的，有品味的，有道德的人是一个回答
不懂行，品味低，无道德的人是另一个回答

你的选择
你也可以找例子

中科院神经所的郭爱克教授，目前并不是院士，
但是你如果看他去年的论文，就会知道他的科学研究好，
就会尊重他

上海二医的王振义发现白血病亚型治疗方法，世界都用
70年代中国中医研究院屠呦呦等发现青蒿素，是目前世界科学和药学界疟疾治疗效果最强的药，中国知道她的人有限，更不是院士）
（最强的抗疟药说法依据：e.g. Nature, 424:957-961)

上路前的第二个临行赠言
著名科学家人不一定好

有好的："古"有Darwin和Wallace互相对待, 今有Ira Herskorwitz对Yasuji Oshima (H & O 分别发现酵母mating type switch。为了让更多人认识到O的贡献，H力促O得2001年Morgan奖)

也有不好的
而且不好的著名科学家不是今天才出现的问题
也不是中国特有的
牛顿好不好，说他为人不好也有基础
"站在巨人肩上"说：和Hook的互相攻击
在calculus发明权上，如何对待Leibnitz

（这样举例是希望在你们如果碰到对你不好的著名科学家的时候，不过分难过，或者对"现代"著名科学家幻灭）

上路前的第三个临行赠言
成功和幸福无一定关系

(或者是我这堂课最后一次批评中国常规"智慧"的机会：人数不少的老师和（比较悲惨地）父母 相信和"教导的定论好像不少定论－－至少在我看来)

"成功" 和 "幸福"没有绝对的方程式.

这个关系对不同的人在不同时候是不同的。如果简单相信这两个必定成正相关，冒的危险不是庸俗就是表明没有成功过。

社会只（或者说多半只）关心你的成功（就是动物的进化到人里面改了一个名词），你得自己照顾你的幸福。

这也许可以作为在你们走上正式研究道路（或者其它职业）以前，提醒小心不要有或者继续对成功和幸福关系有幻觉illusion，幻觉是可以造成幻灭disillusion的原因。

（记住以前多数老师和亲戚的多数有关这个问题的多数话也许帮助不大）

你自己决定做什么如何安排生活和工作

祝愿

你们

如果对生命科学研究感兴趣，

从这个课得到一些背景

It is now your turn to design and carry out 科学研究project

意义，重要性

优雅—elegance
and/or 有趣性

In 10 or 20 years, the work of some of you will be presented here stories to inspire new students to life sciences research

如果有问题

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我在办公室的时候，和学术有关的问题，都会回答，不懂不出来也会回

你们也可以问高年级同学，有过约600学生，我不知道所有的好学生，不过你们自己可以去发现