Cellular and Molecular Biology of the Neuron
Part III
神经系统细胞生物学（三）

张研

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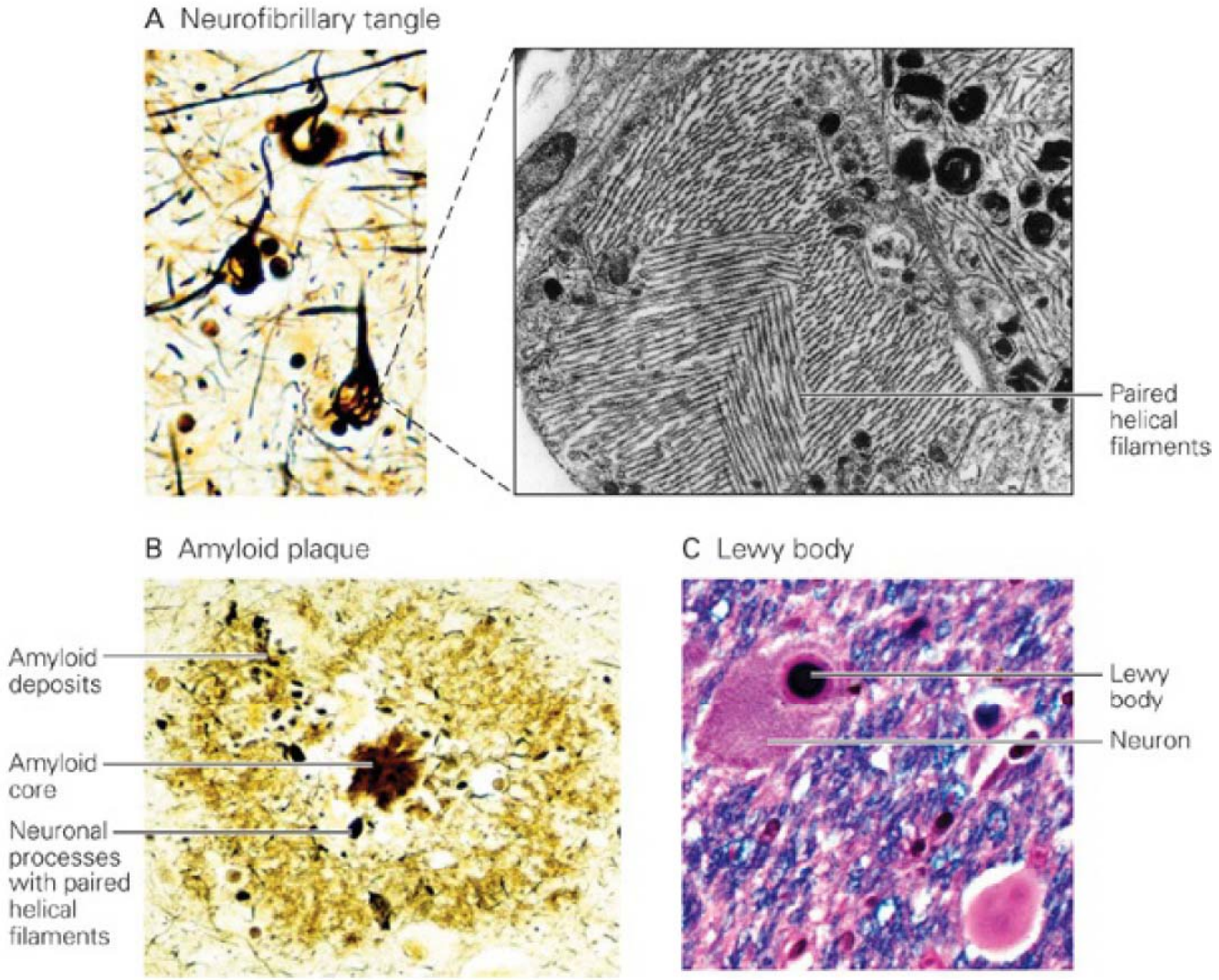
Abnormal aggregates of proteins inside neurons in Alzheimer and Parkinson diseases

阿兹海默症和帕金森氏症神经元内蛋白异常聚集



Studying diseases is a way to understand normal physiology

研究疾病是了解正常生理学的一种途径

Dementia

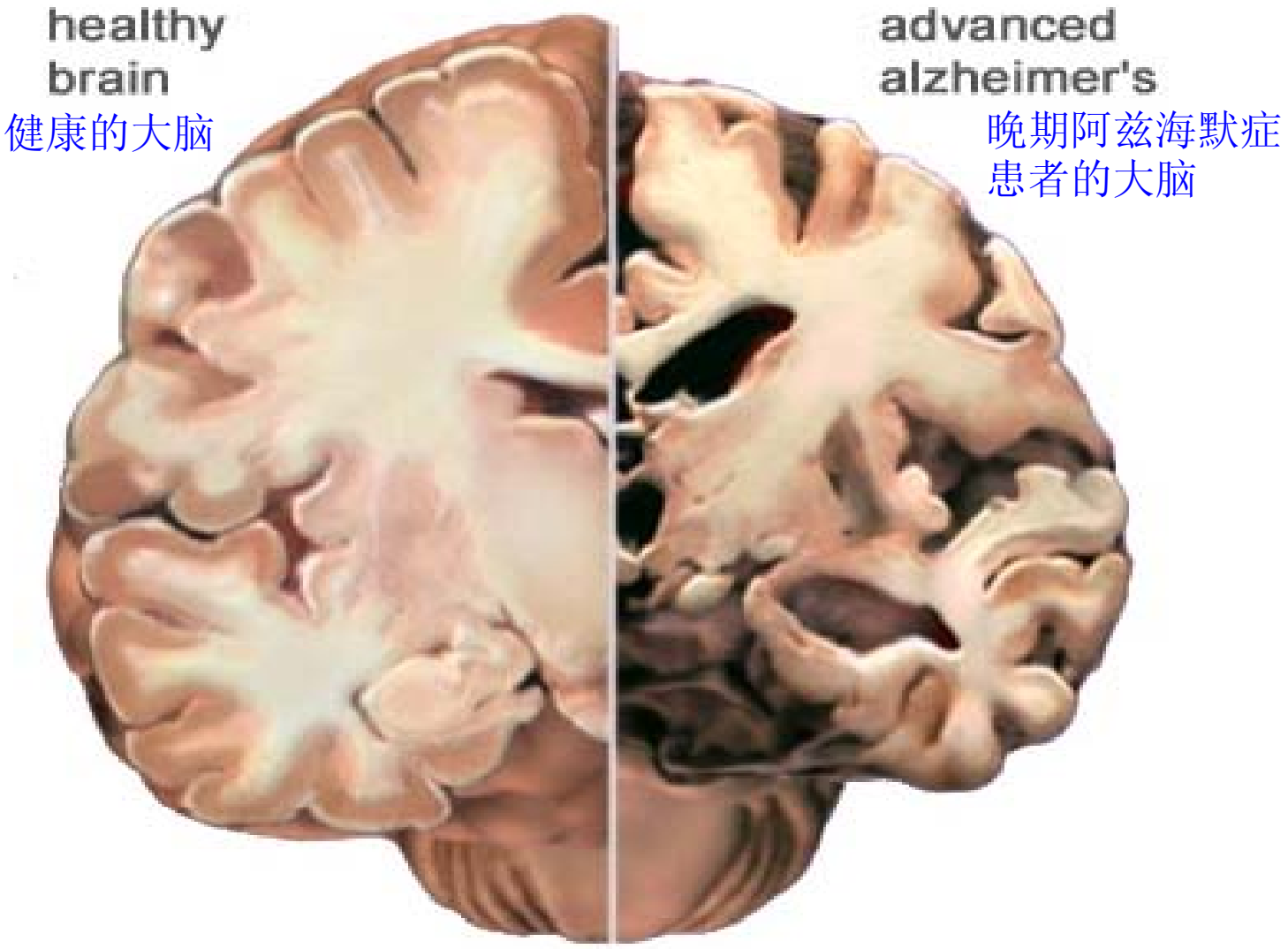
Alzheimer's disease (AD) is the most common form of dementia, a group of conditions that all gradually destroy brain cells and lead to progressive decline in mental function. Vascular dementia, another common form, results from reduced blood flow to the brain's nerve cells. In some cases, Alzheimer's disease and vascular dementia can occur together in a condition called "mixed dementia." Other causes of dementia include frontotemporal dementia, dementia with Lewy bodies, Creutzfeldt-Jakob disease and Parkinson's disease.

痴呆：

阿兹海默症是痴呆的一种常见形式，是脑细胞的逐步受损以及心智功能的进行性衰退。血管性痴呆是其另一种常见形式，由到神经元的血流量减少引起。在某些情况下，阿兹海默症和血管性痴呆会同时发生，即“混合性痴呆”。其他病因造成的痴呆还包括额颞痴呆、路易体痴呆、克雅氏病和帕金森氏症。

Alzheimer's disease is a progressive brain disorder that gradually destroys a person's memory and ability to learn, reason, make judgments, communicate and carry out daily activities. As Alzheimer's progresses, individuals may also experience changes in personality and behavior, such as anxiety, suspiciousness or agitation, as well as delusions or hallucinations.

阿兹海默症是一种进行性的脑功能紊乱，逐渐摧毁一个人的记忆以及学习、推理、判断、交流、执行日常活动的能力。伴随病程，病人还会经历人格和行为的改变，比如焦虑、猜疑、激动，以及妄想或幻觉。

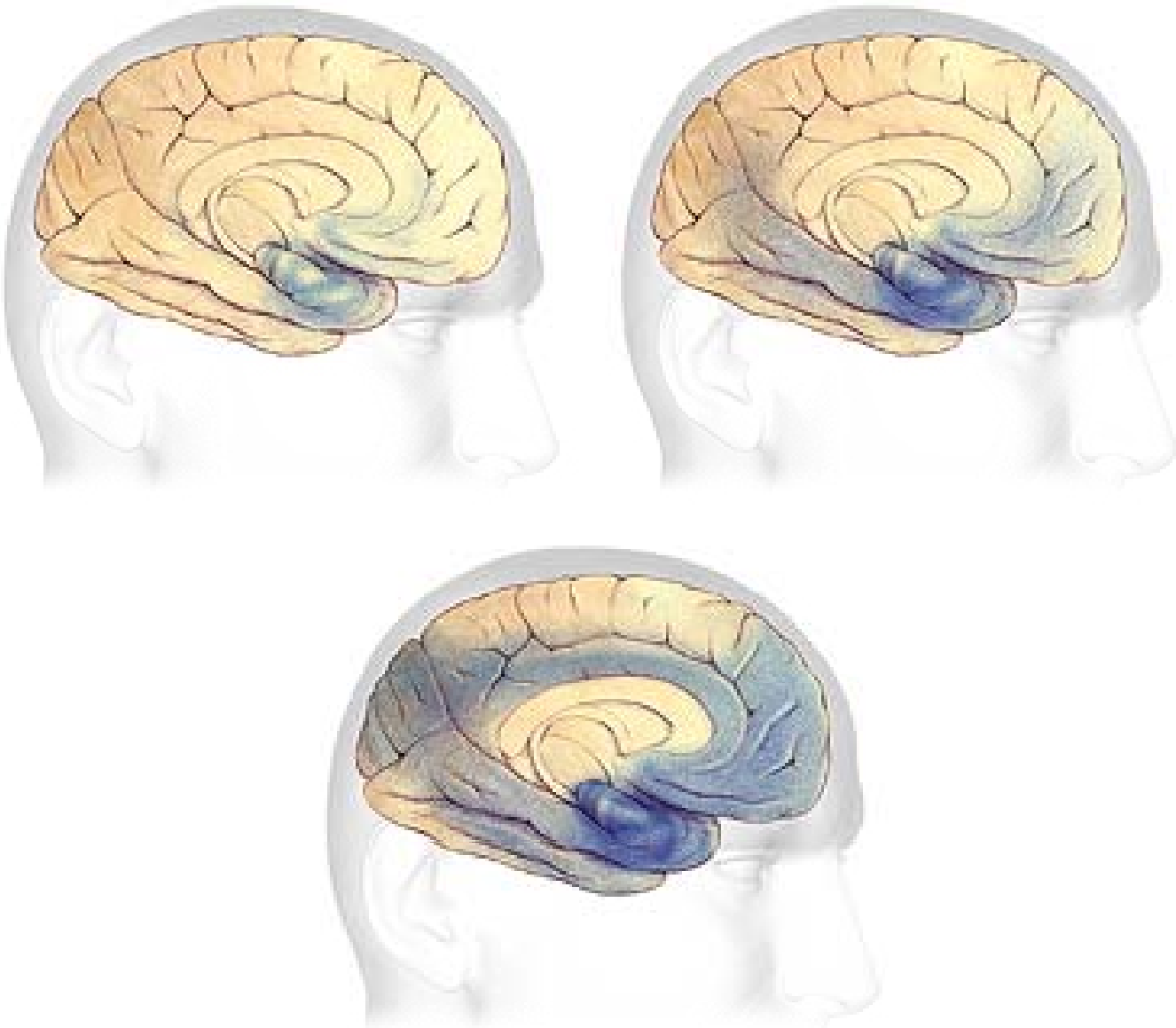

healthy
brain
健康的大脑
advanced
alzheimer's
晚期阿兹海默症
患者的大脑

Progression of Alzheimer’s disease

Alzheimer’s disease advances at widely different rates. The duration of the illness may often vary from 3 to 20 years. The areas of the brain that control memory and thinking skills are affected first, but as the disease progresses, cells die in other regions of the brain. Eventually, the person with Alzheimer’s will need complete care. If the individual has no other serious illness, the loss of brain function itself will cause death.

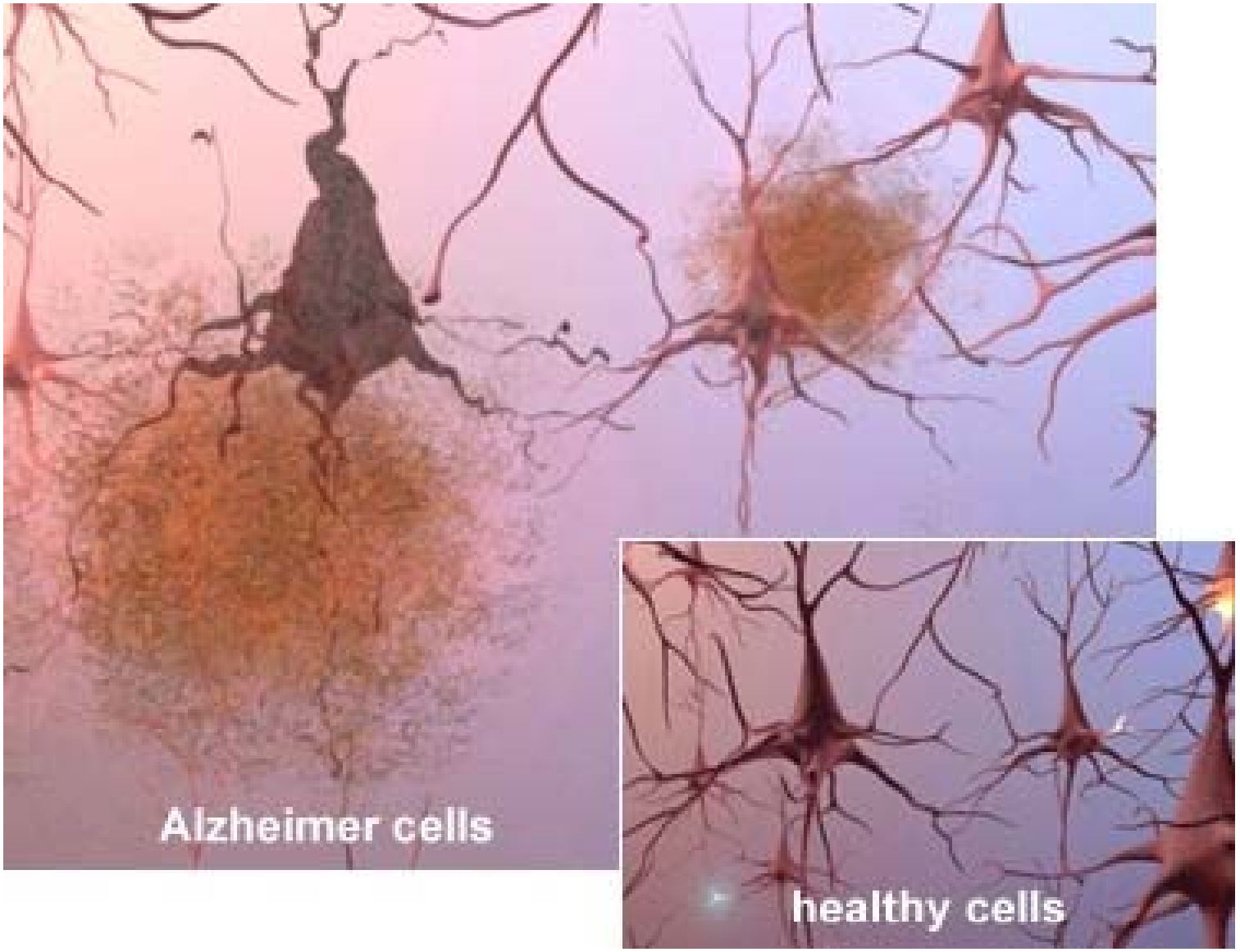
阿兹海默症的进程

阿兹海默症以不同的速度发展，持续的时间3年至20年不等。控制记忆和思考的脑区最先受损，随着病情恶化，其他部位的神经元死亡。最终，阿兹海默症患者需要全面的照顾。如果没有其他严重疾病，脑功能的缺失本身将会致死。



Scientists believe that whatever triggers Alzheimer's disease begins to damage the brain years before symptoms appear. When symptoms emerge, nerve cells that process, store and retrieve information have already begun to degenerate and die. Scientists regard two abnormal microscopic structures called "plaques" and "tangles" as Alzheimer hallmarks. Amyloid plaques (or senile plaques, SPs) are clumps of protein that accumulate outside the brain's nerve cells. Neurofibrillary tangles (NFTs) are twisted strands of another protein that form inside cells. Scientists do not yet know whether plaques or tangles cause Alzheimer's or are a byproduct of some other process.

科学家们认为，在症状出现的数年前，致病因子就开始损坏大脑。当症状出现时，加工、存储、检索信号的神经元已经开始退化和死亡。科学家们认为“斑块”和“缠结”这两种非正常显微结构作为阿兹海默症的标志。淀粉样斑块（或称老年斑，SP）是脑神经细胞外部蛋白的聚集块。神经纤维缠结（NFT）是另一种蛋白在细胞内部扭曲缠绕形成的。科学家们至今不知道这些斑块或缠结是阿兹海默症的致病因还是其他过程的副产品。


Alzheimer cells
healthy cells

Risk factors

Scientists have learned that Alzheimer's disease involves the malfunction or death of nerve cells, but why this happens is still not known. However, they have identified certain risk factors that increase the likelihood of developing Alzheimer's and discovered clues about possible strategies to reduce risk.

风险因素

科学家们发现阿兹海默症包含神经元的功能失常或死亡，但是这些原因并不清楚。然而他们鉴别出一些增加阿兹海默症发生可能性的风险因素以及降低这些风险的线索。

Age

The greatest known risk factor is increasing age, and most individuals with the illness are 65 and older. The likelihood of developing Alzheimer's approximately doubles every five years after age 65. After age 85, the risk reaches nearly 50 percent.

年龄

最重要的一个风险因素就是增长的年龄，大多数患者都在65岁或以上。65岁之后每五年患病概率都会加倍，85岁之后患病概率达到近50%。

Family history and genetics

Another risk factor is family history. Research has shown that those who have a parent or sibling with Alzheimer's are two to three times more likely to develop the disease than those who do not. The more individuals in a family who have the illness, the greater the risk.

Scientists have so far identified one gene that increases risk of Alzheimer's but does not guarantee an individual will develop the disorder. Research has also revealed certain rare genes that virtually guarantee an individual will develop Alzheimer's. The genes that directly cause the disease have been found in only a few hundred extended families worldwide and are thought to account for a tiny percentage of cases. Experts believe the vast majority of cases are caused by a complex combination of genetic and non-genetic influences.

家族史及遗传学

另一个风险因素是家族史。研究表明父母或家族成员患有阿兹海默症的个体，其患病的可能性是普通人的两到三倍。家族中患病人数越多，该个体患病的可能性就越大。

科学家们目前确定一个可以增加患病风险但不会绝对致病的基因。研究揭示某些稀有基因实质上可以导致个体发病。这些直接致病基因仅在全球几百个家庭中发现，占病例中非常小的概率。专家认为，大部分病例还是由遗传和非遗传的复合影响导致的。

Paths to prevention

Genes and environment

Scientists worldwide are looking for other risk factors that may provide opportunities for treatment or prevention. Some of our best information about the relative importance of risk factors we can and can't control comes from studies of identical twins, who are the same age and have the same genes but have different life experiences.

Several twin studies have shown that when one twin develops AD, the other twin is at increased risk but does not always develop the disease. Other studies suggest that even in cases where both twins develop AD, the age where symptoms appear can differ significantly. These results suggest that even when there is a strong genetic influence, other factors can play a major role.

预防途径

遗传和环境

全球的科学家们都在寻找其他风险因素，以期提供治疗和预防的机会。对双胞胎的研究提供了一些最好的可控和不可控的风险因素的相对重要性的信息，他们年龄相同、基因一样，但生活经历不同。

几例双胞胎研究表明，当双胞胎中其中一个患有AD，那么另外一个患病的风险更高但并不一定得病。其他研究表明即使两个人都患病，发病年龄差异也很大。这些结果表明即使在很强的遗传因素影响下，其他因素仍能发挥主要作用。

Head injury

Research is beginning to reveal clues about some potentially controllable risk factors. There appears to be a strong link between serious head injury and future risk of Alzheimer's. It's important to protect your head by buckling up your seat belt, wearing your helmet and fall-proofing your home.

颅脑损伤

研究正在揭示一些潜在可控风险因素的线索。严重的颅脑损伤和未来患病的风险似乎紧密相关。系好安全带、带上头盔、房屋防坠以保护头部还是非常必要的。

Overall brain health

One promising line of research suggests that strategies for overall healthy aging may help keep the brain healthy and may even offer some protection against Alzheimer's. These measures include eating a healthy diet, staying socially active, avoiding tobacco and excess alcohol, and exercising both body and mind.

全脑保护

一个前景光明的研究表明机体健康衰老的策略可能保持大脑的健康，甚至为防御阿兹海默症提供了保护。这些标准包括健康饮食、保持社交活跃、杜绝烟草和过度饮酒，同时要健身健脑。

Heart/head connection

Some of the strongest evidence links brain health to heart health. The risk of developing Alzheimer's or vascular dementia appears to be increased by many conditions that damage the heart and blood vessels, including heart disease, diabetes, stroke and high blood pressure or cholesterol. You should work with your doctor to monitor your heart health and treat any problems that arise.

Autopsy studies provide additional evidence for the heart-head connection. These studies suggest that plaques and tangles are more likely to cause Alzheimer symptoms if strokes or damage to the brain's blood vessels are also present.

心脑联系

还有一些有力的证据建立了颅脑健康与心脏健康的联系。阿兹海默症或血管性痴呆的发病风险似乎会因导致心脏和血管损伤的因素增加，比如心脏病、糖尿病、中风和高血压或高胆固醇。你需要和你的医生协作来监控你的心脏健康以及发生的任何问题。
尸检又为心脑联系提供了其他的证据。这些研究表明如果发生中风或脑血管损伤，斑块和缠结更容易造成阿兹海默症发作。

Myth 1: Memory loss is a natural part of aging.

Reality: In the past people believed memory loss was a normal part of aging, often regarding even Alzheimer's as natural age-related decline. Experts now recognize severe memory loss as a symptom of serious illness.

Whether memory naturally declines to some extent remains an open question. Many people feel that their memory becomes less sharp as they grow older, but determining whether there is any scientific basis for this belief is a research challenge still being addressed.

谬误1：丧失记忆是衰老的自然表现

事实：过去人们认为丧失记忆是衰老的一部分，通常认为阿兹海默症是自然的年龄相关的记忆减退。专家现在认为严重的记忆丧失是严重疾病的症状。
记忆是否会自然的退到某个程度依然是个开放性的问题。许多人感觉随着他们衰老，记忆变得模糊，但是这是否存在理论根据是个科研挑战，需要继续探讨。

The difference between Alzheimer's and normal age-related memory changes

阿兹海默症与正常的年龄相关记忆改变的差异

Someone with Alzheimer's disease symptoms 阿兹海默症	**Someone with normal age-related memory changes** 正常的年龄相关记忆改变
Forgets entire experiences 遗忘全部的经历	Forgets part of an experience 遗忘部分经历
Rarely remembers later 事后很难记得	Often remembers later 事后通常记得
Is gradually unable to follow written/spoken directions 逐渐不能跟随写/说的指导	Is usually able to follow written/spoken directions 通常可以跟随写/说的指导
Is gradually unable to use notes as reminders 逐渐不能利用纸条作为提醒	Is usually able to use notes as reminders 通常可以利用纸条作为提醒
Is gradually unable to care for self 逐渐不能照顾自己	Is usually able to care for self 通常可以照顾自己

Myth 2: Alzheimer’s disease is not fatal.

Reality: Alzheimer's is a fatal disease. It begins with the destruction of cells in regions of the brain that are important for memory. However, the eventual loss of cells in other regions of the brain leads to the failure of other essential systems in the body. Also, because many people with Alzheimer’s have other illnesses common in older age, the actual cause of death may be no single factor.

谬误2：阿兹海默症不致死

事实：阿兹海默症是一种致死的疾病。它开始于脑区中对于记忆重要的细胞的破坏，然而，脑中其他区域细胞的最终死亡导致身体其他系统的故障。此外，因为很多AD患者会有其他老年常见病，所以致死的因素也并不单一。

Myth 3: Drinking out of aluminum cans or cooking in aluminum pots and pans can lead to Alzheimer’s disease.

Reality: Based on current research, getting rid of aluminum cans, pots, and pans will not protect you from Alzheimer’s disease. The exact role (if any) of aluminum in Alzheimer’s disease is still being researched and debated. However, most researchers believe that not enough evidence exists to consider aluminum a risk factor for Alzheimer’s or a cause of dementia.

谬误3：用铝罐喝水或者用铝壶铝锅烹饪导致阿兹海默症

事实：基于当前的研究，不用铝罐、铝壶、铝锅并不能使你免于罹患阿兹海默症。在阿兹海默症中铝的确切功能仍在研究和争论中，然而多数学者认为铝作为阿兹海默症或痴呆病因的证据并不充分。

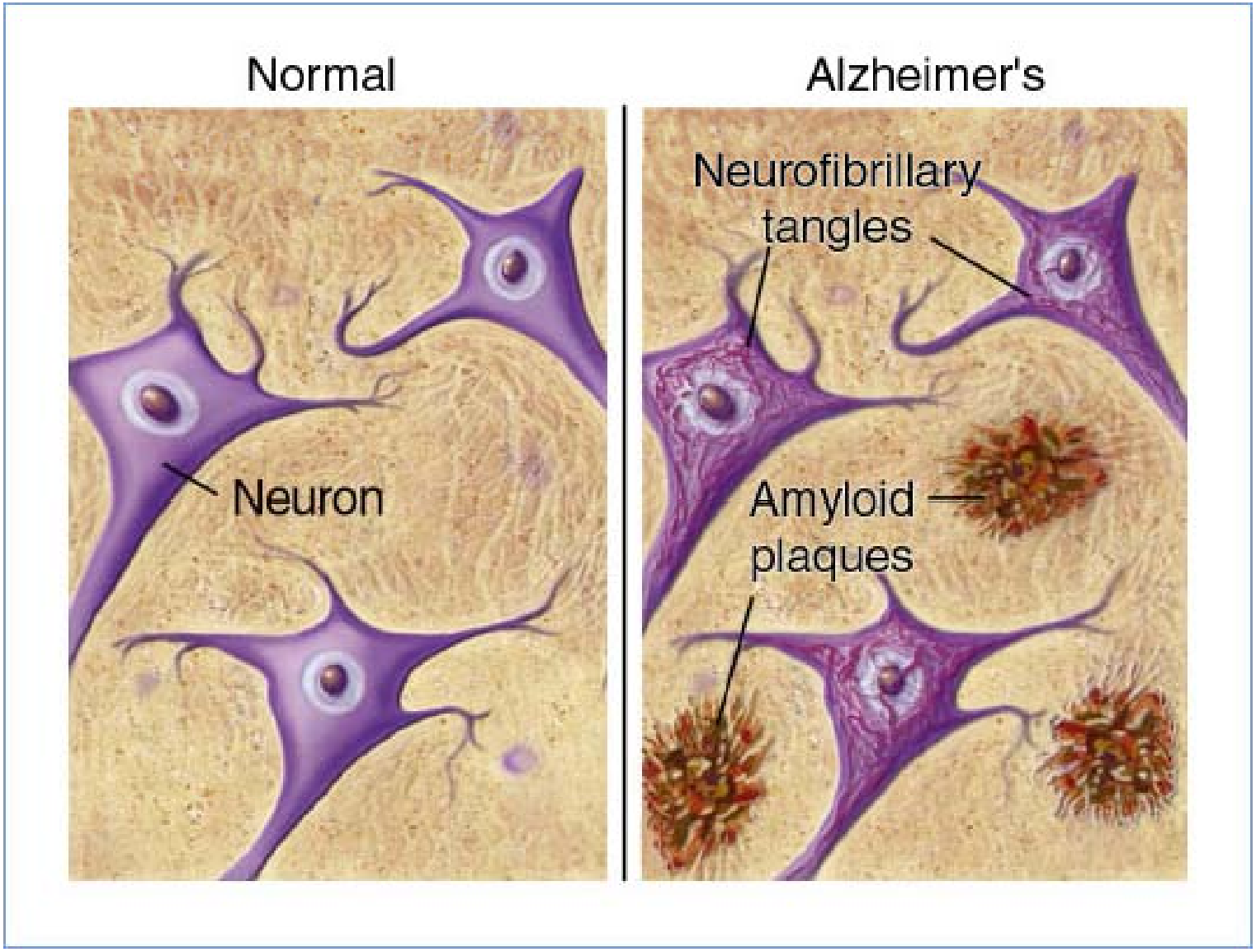
Myth 4: There are therapies available to stop the progression of Alzheimer's disease.

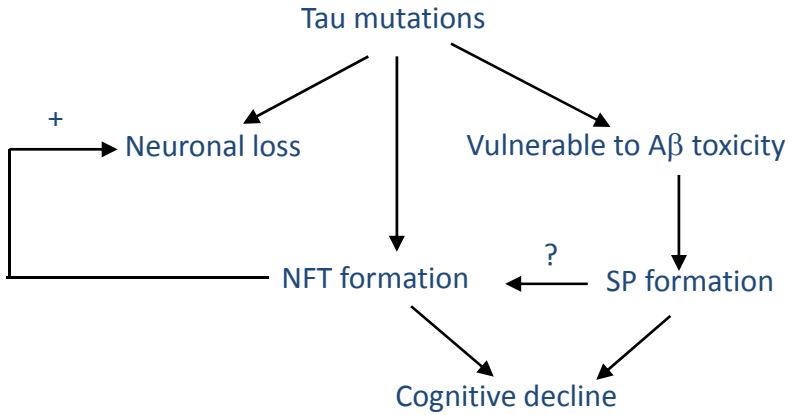
Reality: At this time, there is no medical treatment to cure or stop the progression of Alzheimer's disease. FDA-approved drugs may temporarily improve or stabilize memory and thinking skills in some individuals.
谬误4：存在可用的阻止阿兹海默症恶化的治疗方案
事实：现在并没有治疗可以根治或阻止阿兹海默症病情的恶化。FDA认证的药物只能暂时提高或稳定某些患者的记忆以及思考能力。

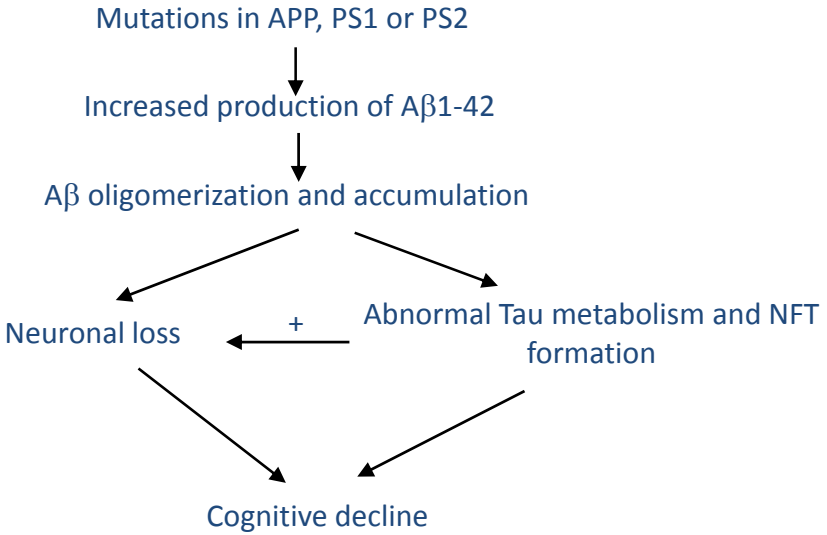
Currently, there is no cure for Alzheimer's. But drug and non-drug treatments may help with both cognitive and behavioral symptoms.
Researchers are looking for new treatments to alter the course of the disease and improve the quality of life for people with dementia.
Cholinesterase Inhibitors　　Memantine　　Vitamin E

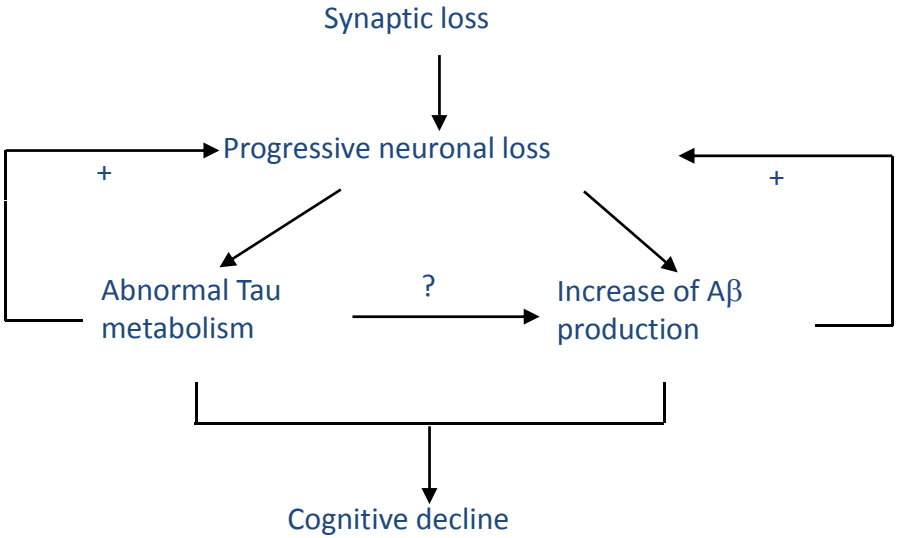
眼下，阿兹海默症无药可治。但是有一些药物或者非药物处理可以改善认知和行为症状。
研究者试图找到新的治疗方法来改变病程，提高痴呆患者的生活质量。

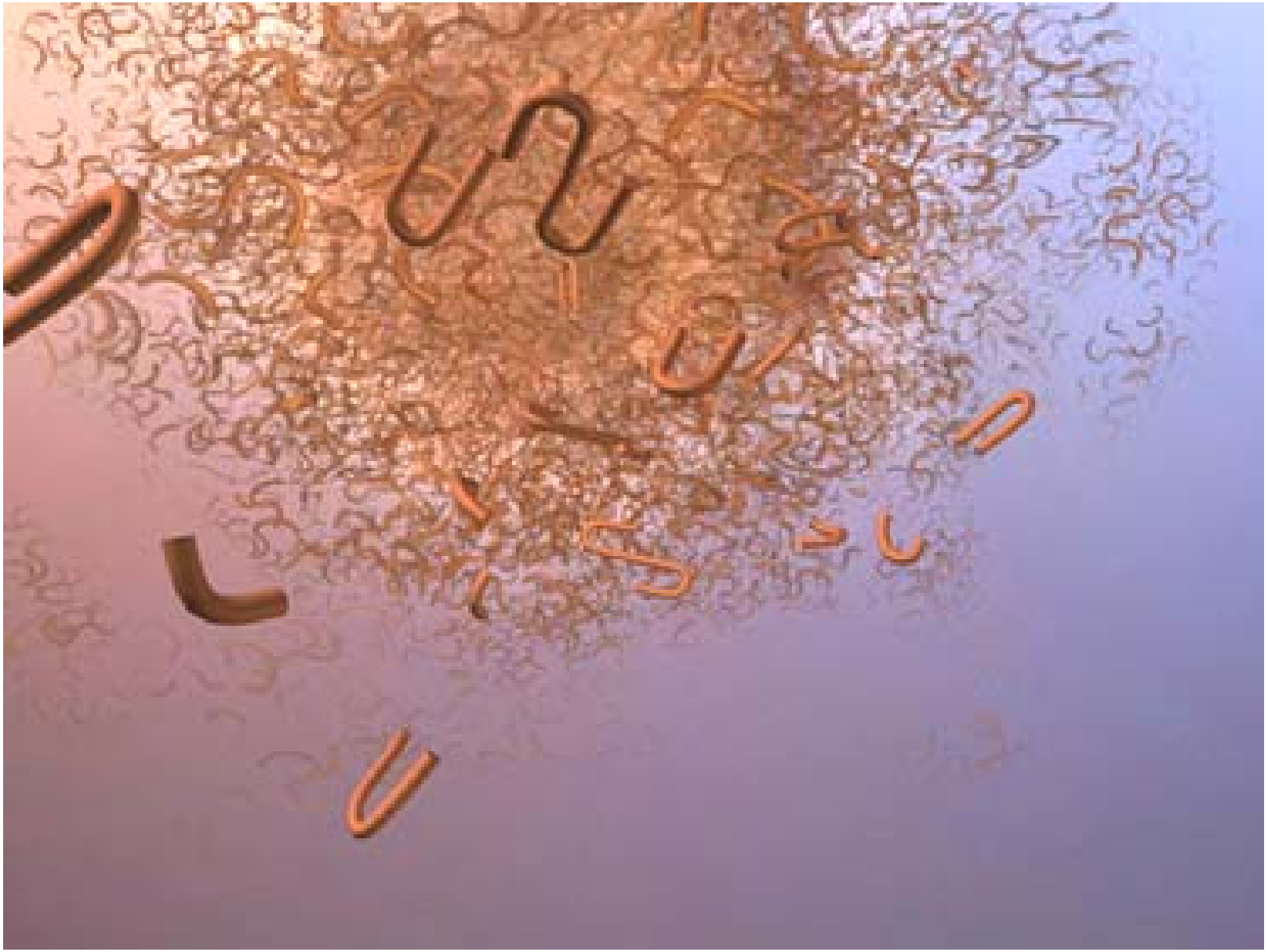
胆碱酯酶抑制剂　　美金刚胺　　维他命E


Normal
Alzheimer's
Neuron
Neurofibrillary tangles
Amyloid plaques


Tau mutations
+
Neuronal loss
Vulnerable to Aβ toxicity
?
NFT formation
SP formation
Cognitive decline


Mutations in APP, PS1 or PS2
Increased production of Aβ1-42
Aβ oligomerization and accumulation
Neuronal loss
+
Abnormal Tau metabolism and NFT formation
Cognitive decline


Synaptic loss
Progressive neuronal loss
+
+
Abnormal Tau metabolism
?
Increase of Aβ production
Cognitive decline



Occasionally, cells produce abnormal proteins that can settle in body tissue, forming deposits and causing disease. When these deposits of abnormal proteins were first discovered, they were called *amyloid*, and the disease process *amyloidosis*.
偶尔地，细胞产生的正常的蛋白会在细胞内“安家”，形成沉积、致病。当这些正常蛋白的沉积第一次被发现时，被命名为“淀粉状蛋白”，这个过程叫“淀粉样变性”。

Senile (or neuritic) plaques (SPs) are the extracellular proteinacous deposits found in AD patient brains.
老年斑是存在于AD患者脑部胞外蛋白沉积。

In addition to human, extracellular SPs are also found in other long-lived mammals, such as some non-human primates like Cheirogelidae, Callitricadae, Cebidae and Pogidae (Struble et al., 1984; Gearing et al., 1995; Gearing et al., 1997), domestic dogs (Cummings et al., 1996; Tekirian et al., 1996), cats (Cummings et al., 1996) and polar bears (Cork et al., 1988; Tekirian et al., 1996). However, common laboratory rats and mice do not have natural accumulation of amyloid with age (Jucker et al., 1994).
除人类之外，胞外老年斑还在其他长寿的哺乳动物中存在，比如非人灵长类(Struble et al., 1984; Gearing et al., 1995; Gearing et al., 1997)、家犬(Cummings et al., 1996; Tekirian et al., 1996)、猫(Cummings et al., 1996; Tekirian et al., 1996)、北极熊bears (Cork et al., 1988; Tekirian et al., 1996)。然而，常见的实验室的大鼠和小鼠随年龄不会有自然的淀粉样沉积age (Jucker et al., 1994)。

Amyloid precursor protein (APP), cloned in 1987 (Kang et al., 1987), is a type-1 transmembrane glycoprotein with ten isoforms generated by alternative mRNA splicing. APP is encoded by a single gene at human chromosome 21 containing 18 exons (Kang et al., 1987; Goate et al., 1991). APP has a signal peptide, a large extracellular N terminal domain and a small intracellular C terminal domain, a single transmembrane domain and an endocytosis signal at the C terminal.

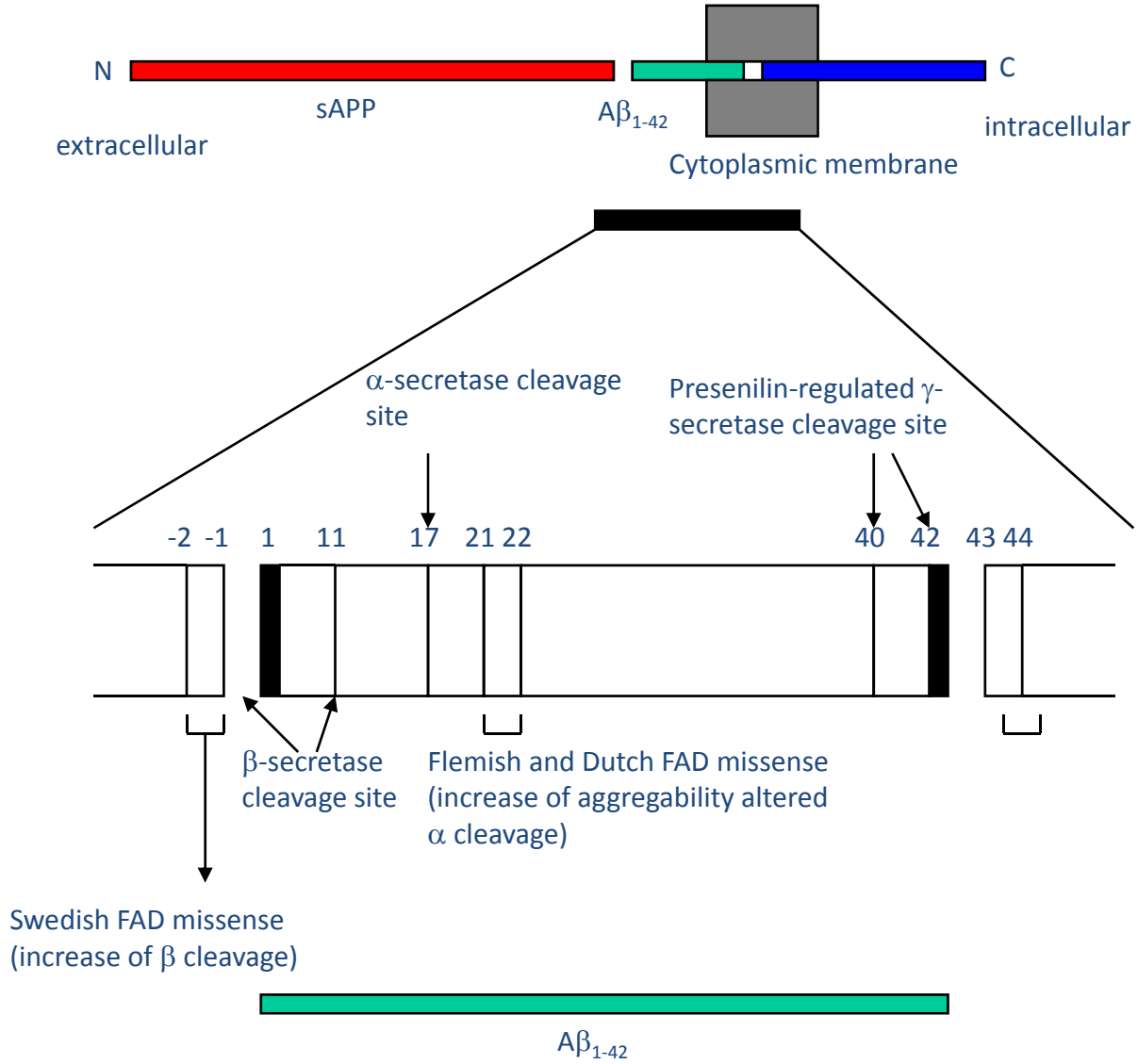
Among ten isoforms of APP ranging from 563 to 770 amino acids, the major ones are APP770, APP751 and APP695. Isoform APP695 is expressed at high levels in the brain.

淀粉样前体蛋白在1987年被克隆出来，是I-型跨膜糖蛋白，经mRNA的选择性剪切形成10种亚型。APP由人体21号染色体上具有18个外显子的单基因编码，有一个信号肽，具有巨大的N端胞外段和小的C端胞内段、一个跨膜区和C端的内吞信号。

在这10种剪切体中，APP有563和770个氨基酸不等，主要的是 APP770, APP751 和 APP695。APP695在脑内高表达。

Under physiological conditions, newly synthesized APP matures in the endoplasmic reticulum and the Golgi, acquiring N- and O-linked glycosylation and phosphorylation. APP is located in the neuronal cell bodies as well as axons. APP may play a role in neurite outgrowth and extension, and probably in synaptic transmission and maintenance of axons (Yamaguchi et al., 1990; Yamaguchi et al., 1994). In addition, APP has been suggested to have neuroprotective function or neurotrophic roles (Mattson et al., 1993b). APP knockouts are fertile (Zheng et al., 1996). Neuroanatomical studies of APP knockout mouse brains show no significant differences relative to the wild-type control brains (Zheng et al., 1996).

在生理条件下，新合成的APP在内质网和高尔基体成熟，获得N-连接和O-连接的糖基化和磷酸化。APP定位在神经元胞体和轴突，在神经突的生长、外展，可能在突触传递、轴突维持中发挥作用(Yamaguchi et al., 1990; Yamaguchi et al., 1994)。此外，APP还被证明有神经保护和神经营养的功能 (Mattson et al., 1993b)。APP敲除的鼠多产(Zheng et al., 1996)。神经解剖学对APP敲除的鼠脑研究表明其与野生型对照的鼠脑没有显著差异(Zheng et al., 1996)。


N
C
sAPP
Aβ1-42
extracellular
intracellular
Cytoplasmic membrane
α-secretase cleavage site
Presenilin-regulated γ-secretase cleavage site
-2 -1 1 11 17 21 22 40 42 43 44
β-secretase cleavage site
Flemish and Dutch FAD missense (increase of aggregability altered α cleavage)
Swedish FAD missense (increase of β cleavage)
Aβ1-42

The exact location of α-secretase activity is still unknown, although some data suggest that α-cleavage occurs mainly at trans-Golgi or plasma membrane (Kuentzel et al., 1993). One possible explanation for the uncertainty about the localization of α-secretase is that there may be more than one enzyme with the α-secretase activity. The candidates for α-secretase are two members of the family of disintegrin and metalloprotease ADAM: tumour necrosis factor- (TNF)-converting enzyme (TACE or ADAM-17) and ADAM-10.

β-site APP cleaving enzyme (BACE or Asp2) has been suggested to be responsible for β-secretase activity. BACE is a member of pepsin family of aspartyl proteases (Vassar et al., 1999).

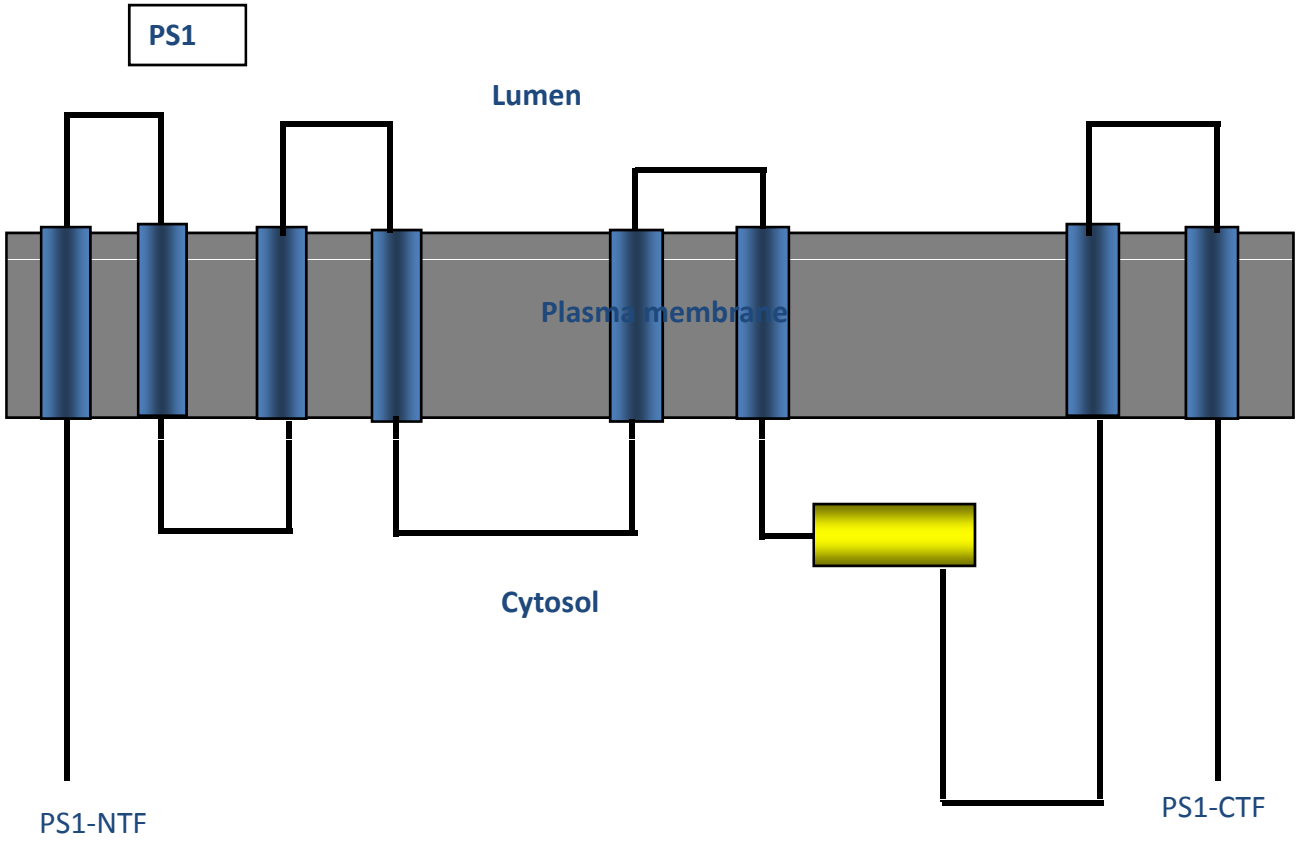
α分泌酶发挥活性的确切位置依然未知，尽管一些数据显示α剪切发生在反式高尔基或者质膜(Kuentzel et al., 1993)。一个对位置不确切的可能解释是参与α分泌酶的活动的酶不仅一种。 α分泌酶可能是解聚酶和金属蛋白酶ADAM家族中的两种成员：肿瘤坏死因子转化酶（TACE或ADAM-17）和ADAM-10。
β位点的APP剪切酶 (BACE or Asp2) 被证实负责β分泌酶的活动。BACE是天冬氨酰蛋白酶中胃蛋白酶的一个成员 (Vassar et al., 1999)。

Recent studies suggest that γ-secretase may not be a single protein but rather mediated by a complex of a number of proteins. γ-secretase activity happens when APP is cleaved within the complex containing presenilin, APP binding proteins Nicastrin, Aph-1 and Pen-2 (Yu et al., 2000; Chen et al., 2001; Chung and Struhl, 2001; Satoh and Kuroda, 2001; Hu et al., 2002).

There are two proposed β- and γ-secretase pathways. One is called the endosomal/lysosomal pathway. APP is endocytosed and delivered to endosomes and lysosomes where β- and γ-secretase cleavages occur. The other pathway suggests that Aβ generation occurs in the endoplasmic reticulum and Golgi-derived vesicles (Chyung et al., 1997; Sinha and Lieberburg, 1999).

日前研究表明，γ分泌酶并不是单一的蛋白质而是蛋白复合体，当APP由早老素、APP结合蛋白Nicastrin、Aph-1 and Pen-2 组成的复合体剪切时(Yu et al., 2000; Chen et al., 2001; Chung and Struhl, 2001; Satoh and Kuroda, 2001; Hu et al., 2002)，γ分泌酶活性产生。

β分泌酶和γ分泌酶有两种推测的通路。一种是内含体/溶酶体通路。APP被β分泌酶和γ分泌酶剪切后，APP被内吞运输到内含体和溶酶体。其他途径表明，Aβ的生成发生在内质网和高尔基体来源的囊泡中 (Chyung et al., 1997; Sinha and Lieberburg, 1999)。


PS1
Lumen
Plasma membrane
Cytosol
PS1-NTF
PS1-CTF

Introduction to PD
帕金森氏症介绍

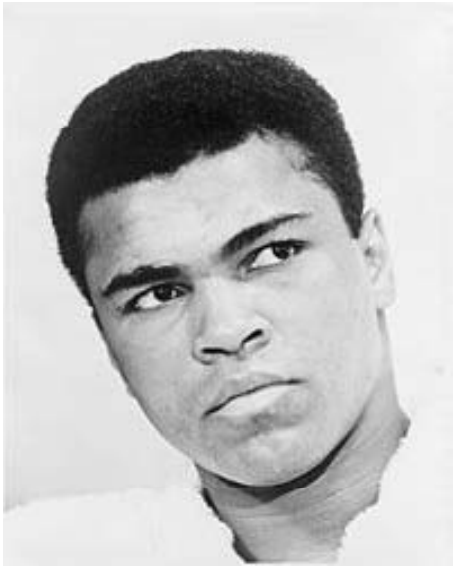
- Belongs to movement disorders
  属于运动系统疾病
- Impairs motor skills and speech
  损害运动功能与语言功能
- Characterized by muscle rigidity, tremor, postural abnormalities, gait abnormalities, a slowing of physical movement (bradykinesia) and a loss of physical movement (akinesia) in extreme cases.
  特征为肌肉僵直、震颤、姿势异常、步态异常、运动迟缓，极端情况下不能运动

The disease is named after English apothecary James Parkinson, who made a detailed description of the disease in his essay: "An Essay on the Shaking Palsy" (1817).

该病以英国药剂师James Parkinson命名，在他的文章“An Essay on the Shaking Palsy”（1817年）第一次被详细描述。

Jean-Martin Charcot made important contributions to the understanding of the disease and proposed its current name honoring James Parkinson. The term “Parkinson’s disease” was coined by Charcot.

Jean-Martin Charcot 对于该病的理解和命名做出了巨大的贡献。"帕金森氏症"的名字由Charcot提出。



Muhammad Ali
3 time World Heavyweight Champion
BBC: Sportsman of the Century
Developed PD in1984

穆罕默德·阿里
三次世界拳击冠军
BBC：世纪最佳运动员
1984年患帕金森氏症

Michael J. Fox 迈克尔·J·福克斯
Back to the future 回到未来
Spin City 政界小人物
Won 3 Emmy Awards 3次获得艾美奖
Diagnosed with PD in 1991 1991年患帕金森氏症
On March 5, 2010, Sweden's Karolinska Institutet gave him a *honoris causa* doctorate for his work in advocating a cure for Parkinson's disease
2010年3月5日，因其对帕金森氏症治疗所做的贡献，瑞典卡罗琳斯卡医学院授予他荣誉博士

Early descriptions 早期描述

- There are some early sources which talk about symptoms that are coherent with PD. An Egyptian papyrus from the 12th century B.C. talks about a king drooling with age and the Bible has references to tremor. An early ayurvedic medical treatise dating back to the 10th century B.C. describes a disease that evolves with tremor, lack of movement, drooling and other symptoms of PD.

有一些早期的资料讨论与PD一致的症状。公元前12世纪的埃及纸莎草记录了一个国王随着变老流口水以及圣经对震颤的引用。早期可追溯到公元前10世纪的阿育吠陀医学论文描述了一种随进程表现震颤、运动不足、流口水等帕金森病的疾病。

- This disease was treated with remedies derived from the mucuna（黎豆属） family, which is rich in L-DOPA. Galen writes on a disease which most surely is PD when he describes tremors that occur only at postural changes and paralysis.

这种疾病的治疗疗法源自于黎豆属(黎豆属)家族，富含左旋多巴。盖伦描写的一种疾病很大可能是PD，这种病人在体位变化和麻痹时震颤。

- After Galen there are no references known to be related to PD until the 17th century. In this and the following century different authors write about some of the elements of the disease, preceding the description by Parkinson.

在盖伦之后直到17世纪才出现PD相关文献。在这个和下个世纪，不同作者都写过关于该疾病的一些方面，这先于帕金森的描述。

- First speculations of the anatomical substrate of PD were made 80 years after Parkinson's essay, when Brissaud proposed that the disease had its origin in the subthalamus and might be caused by an ischemic lesion. In 1912 Frederic Lewy described a pathologic finding in affected brains, later named "Lewy bodies".

第一个关于PD的解剖基础的构想是在帕金森发出文章的80年之后，Brissaud提出这种疾病有它的起源在丘脑底部和可能造成的缺血性病变。1912年弗雷德里克·路易描述了一个病患脑中的病理发现，后来命名为“路易小体”。

- Konstantin Tretiakoff in 1919 discovered that the substantia nigra was the main cerebral structure affected, but it was not widely accepted until further studies by Hassler in 1938. The underlying biochemical changes in the brain were identified in the 1950s due largely to the work of Arvid Carlsson on the neurotransmitter dopamine and his role on PD. He later won a Nobel Prize for his work.

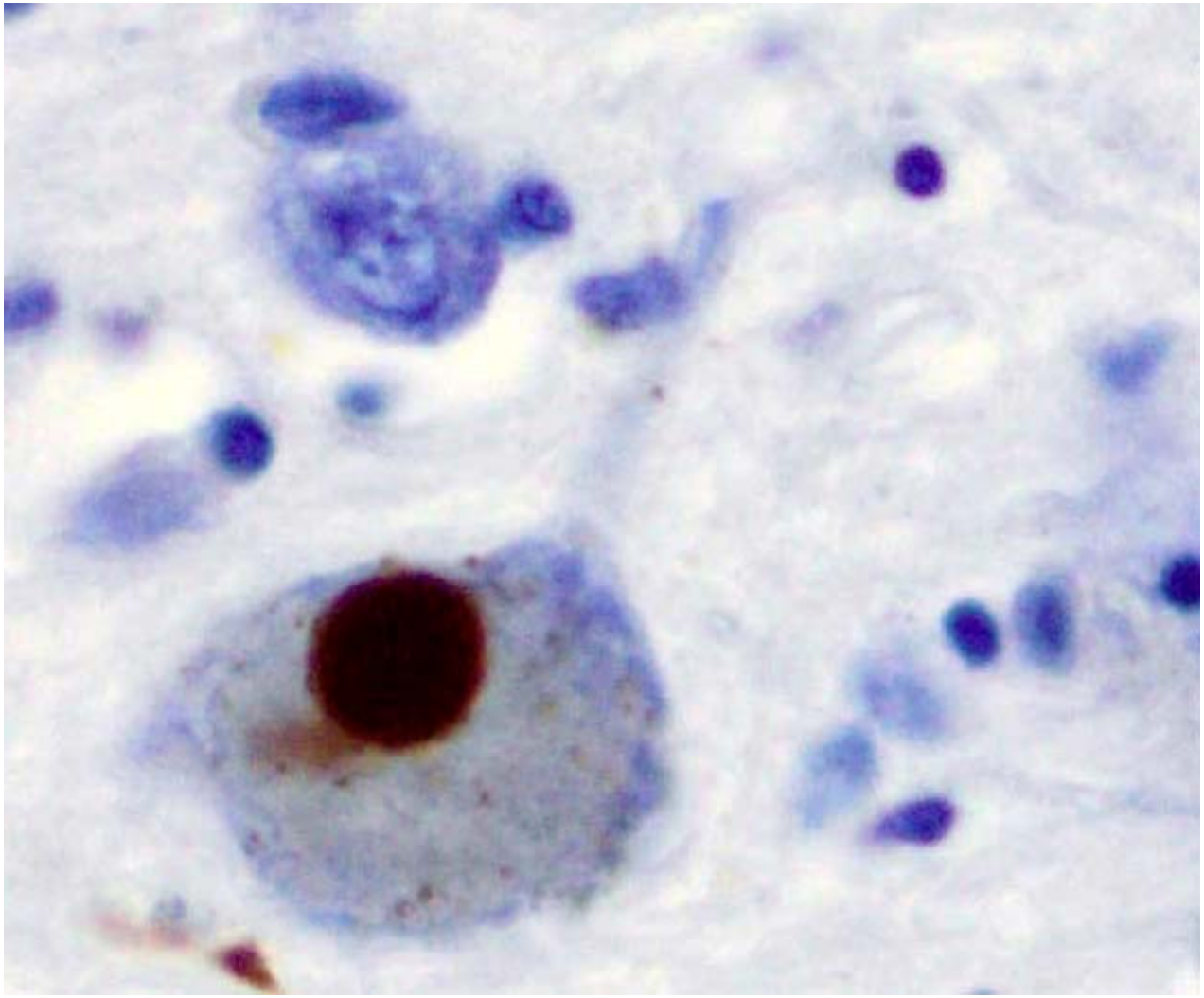
1919年Konstantin Treiakoff发现黑质是主要受影响的大脑结构，但这个观点并不被广泛接受，一直到1938年由哈斯勒进一步的研究被广泛接受。在大脑中潜在的生物化学变化被确定在1950年代，主要是Arvid Carlsson在神经递质多巴胺以及它在PD中的功能的工作。他后来也因此获得诺贝尔奖。

While levodopa was first synthesized in 1911 by Funk, it received little attention until the mid 20th century. It entered clinical practice in 1967, and the first large study reporting improvements in patients with Parkinson's disease resulting from treatment with levodopa was published in 1968. Surgery for tremor was initiated in 1939 and was improved for over 20 years, but the arrival of levodopa reduced its use dramatically. By the late 1980s deep brain stimulation emerged as a possible treatment and it was approved by the FDA in 1997.

尽管在1911年左旋多巴由Funk首次合成，却没有受到多少关注，一直到20世纪中期。它在1967年进入临床实践，患者用左旋多巴治疗改善帕金森氏症的第一个大型研究报告于1968年出版。治疗震颤的外科手术开始于1939年，随后的20年不断在改进，但左旋多巴的到来大大减少了它的使用。到80年代末，深部脑刺激成为可能的治疗，并于1997年获得FDA批准。

Lewy bodies: α-synuclein

路易小体： α-共核蛋白



- According to its pathophysiology PD is considered a synucleinopathy due to its abnormal accumulation of the α-synuclein protein in the brain in the form of lewy bodies.

  根据其病理生理学特征，PD被认为是共核蛋白病，因为α-共核蛋白在脑内异常聚集形成路易小体。

- Non-motor symptoms, which include autonomic dysfunction, cognitive and neurobehavioral problems, and sensory and sleep difficulties, are also common but are under-appreciated.

  非运动症状，包括自主神经功能障碍、认知和神经行为问题、感觉和睡眠困难，很常见但却不被重视。

- Animal model: MPTP (**1-甲基-4-苯基-1,2,3,6-四氢吡啶**), MPPP

  动物模型：MPTP，MPPP

Motor symptoms 运动症状

- tremor, rigidity, bradykinesia and postural instability.

  震颤、僵直、运动徐缓和姿势不稳

- Forward-flexed posture

  身体前倾

- use of small steps when walking

  小步伐走路

Neuropsychiatric symptoms
神经精神病学性状

- cognition, mood and behavior problems
  认知、情绪、行为问题
- A very high proportion of sufferers will have mild cognitive impairment as the disease advances.
  随着病情的发展，很高比例的患者会有轻度认知障碍
- impaired set shifting, poor problem solving, and fluctuations in attention.
  定势转换受损 、解决问题能力变差、注意力不集中
- memory problems; specifically in recalling learned information.

  记忆问题，尤其是回忆学过的信息

- Deficits tend to aggravate with time, developing in many cases into dementia. A person with PD has a six-fold increased risk of suffering dementia.

  能力缺陷会随着时间加剧，大部分情况下发展为痴呆，PD患者会有6倍的风险患痴呆症

- Most frequent mood difficulties include depression, apathy, anxiety and obsessive-compulsive behaviors.

  常见的情绪障碍包括抑郁、冷漠、焦虑和强迫行为

- Psychotic symptoms are common in later PD. Symptoms of psychosis are either hallucinations, or delusions.

  精神病症状在晚期PD较为常见，为幻觉或妄想

- Sleep problems: REM sleep disorder, insomnia.

  睡眠问题：快动眼睡眠障碍，失眠

- Changes in perception include reduced sense of smell and sensation of pain.

  知觉变化包括嗅觉、痛觉不敏感

Prognosis 预后

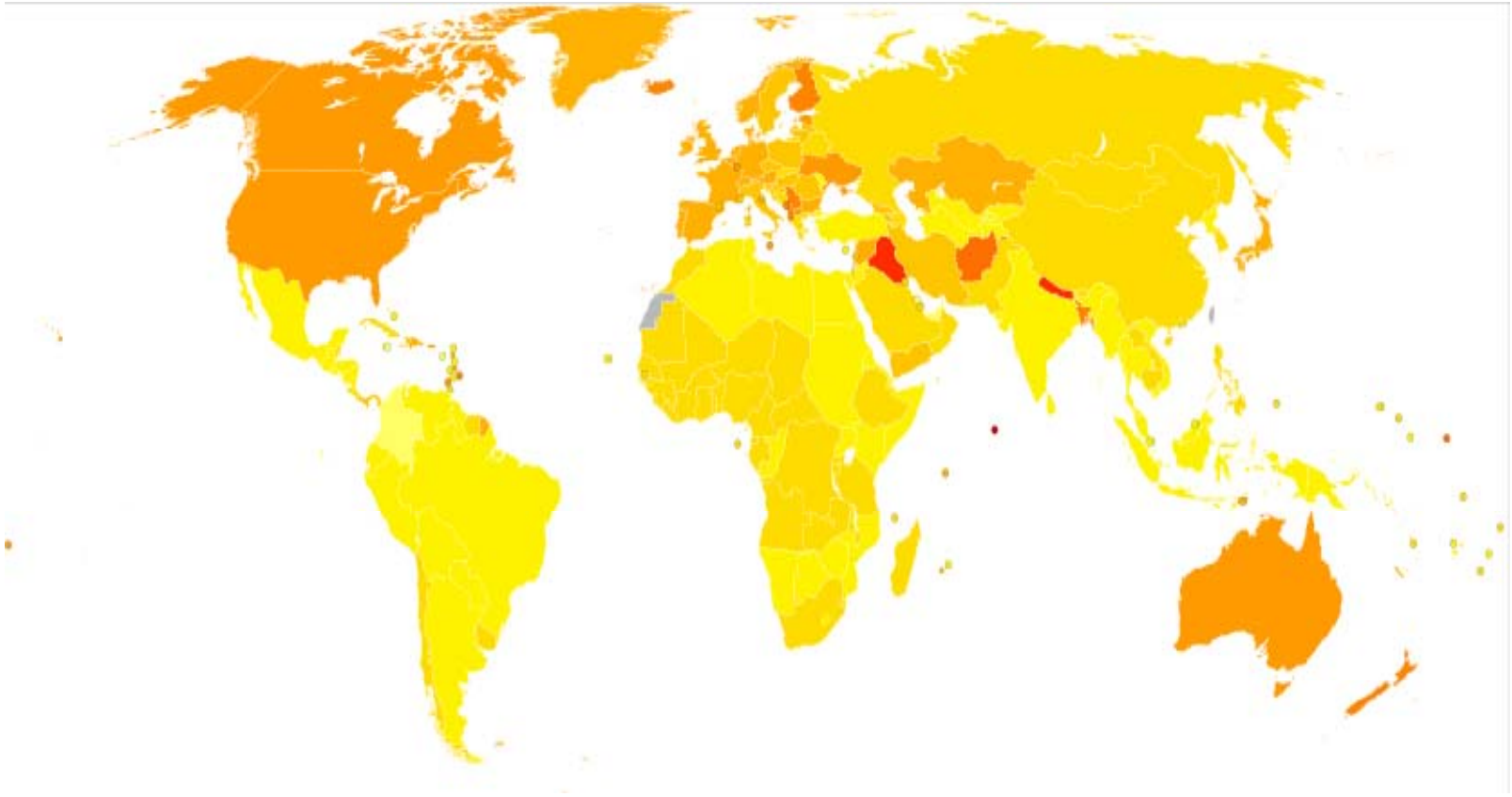
- Untreated patients are expected to lose independence after 8 years and be bedridden after 10 years.

  没有接受治疗的患者预测8年后不能自理，10年后卧床不起
- Different studies of the history of the disease on people taking L-DOPA have found that the mean progression of symptoms to a stage of high dependency of subjects may take around 15 years. However it is hard to predict what course the disease will take for an individual.

  根据患者服用左旋多巴的研究发现，达到高度依赖大概需要15年，但很难预测个体进程
- Age is the best predictor of disease progression. Rate of motor decline is greater in those with less impairment at diagnosis while cognitive impairment is more frequent in those who are over 70 years of age at symptoms onset.

  年龄是预知病情的最好指标。认知损伤更轻的患者运动功能减退的比例更大，70岁及以上发病的患者发生认知损伤更频繁。

Epidemiology 流行病学



Risk and protective factors
风险因素和保护因素

- MPTP injections produce a range of symptoms similar to PD as well as a selective damage to the dopaminergic neurons in the substantia nigra. This has led to theorizing that exposure to some environmental toxins may increase the risk of suffering PD.

注射MPTP产生一系列类似于帕金森病的症状，以及选择性黑质多巴胺能神经元损伤。可以得出接触到一些环境毒素可能会增加罹患PD的风险的结论。

- Toxins that have been consistently related to the disease are certain pesticides and herbicides, with exposure doubling the risk of having PD. Conversely indirect measures of exposure to such toxins, such as living in rural environments have also been found to increasing the risk of PD.

某些杀虫剂和除草剂一直与PD相关，暴露其中患PD的风险会加倍。相反地，间接在这些毒素中的暴露（如生活在农村环境中），也会增加患PD的风险。

- Heavy metals exposure has also been proposed to increase the risk of PD, being its hypothetical mechanism their accumulation in the substantia nigra during the course of the disease, however studies on the issue have been inconclusive.

暴露于重金属也被推测增加患有PD的风险，其假想机制是重金属会在发病过程中在黑质中累积，然而相关研究一直没有定论。

A protective effect of tobacco has been consistently found in epidemiological studies. The basis for such effect is not known but possibilities include an effect of nicotine as dopamine stimulant.
在流行病学研究中频繁发现烟草具有保护作用。该效果的机制尚不明确，但可能是尼古丁作为多巴胺兴奋剂的作用。

Caffeine consumption has also been proposed to protect from PD, but the hypothesis requires further validation.
摄入咖啡因也被提出可以防止患上PD，但假设需要进一步验证。

Antioxidants, such as vitamin C and D, have been proposed to protect against the disease but results of studies have been contradictory and their positive effect is not proven.
抗氧化剂，例如维生素C和D，被提出可以预防该病。但结果研究矛盾，其积极作用也尚未被证明。

Regarding fat and fatty acids, the results on their relationship with PD have been contradictory, with both protective, risk enhancing or no effects.
There have also been some preliminary indications of a possible protective role of estrogens and anti-inflammatory drugs.
脂肪和脂肪酸与帕金森病关系矛盾，可能是保护或增强风险或根本没有作用。
也有一些初步迹象表明雌激素和抗炎药物具有保护作用。

Causes of PD PD病因

- A small proportion of cases is known to be originated in genetic factors.

  小部分是由遗传因素决定的
- PD traditionally has been considered a non-genetic disorder, however around 15% of patients have a first-degree relative who also has the disease. At least between 5 and 10% of the patients are now known to have monogenic forms of the disease. Other genes act as risk factors for sporadic cases of the disease.

  传统上PD被认为是一种非遗传性疾病,但是大约15%的病人都有一级亲属也有这种疾病。至少5%到10%的病人目前已知是单基因致病。也有其他基因是散发病例的风险因素。

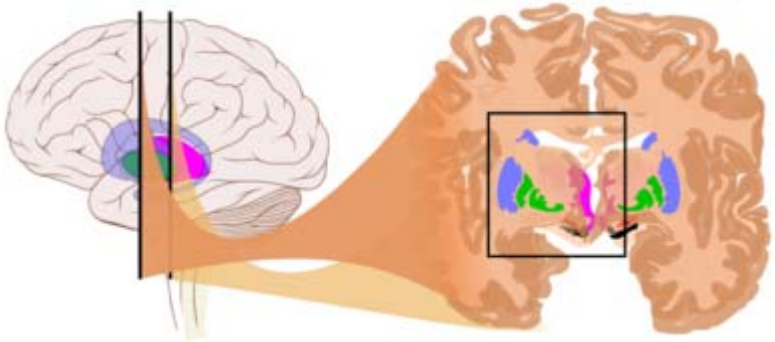
- Genes conclusively identified are α-synuclein (SNCA), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or dardarin) , PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2. With the exception of LRRK2, they account for a small minority of cases of PD. Most studied PD-related genes are SNCA and LRRK2.

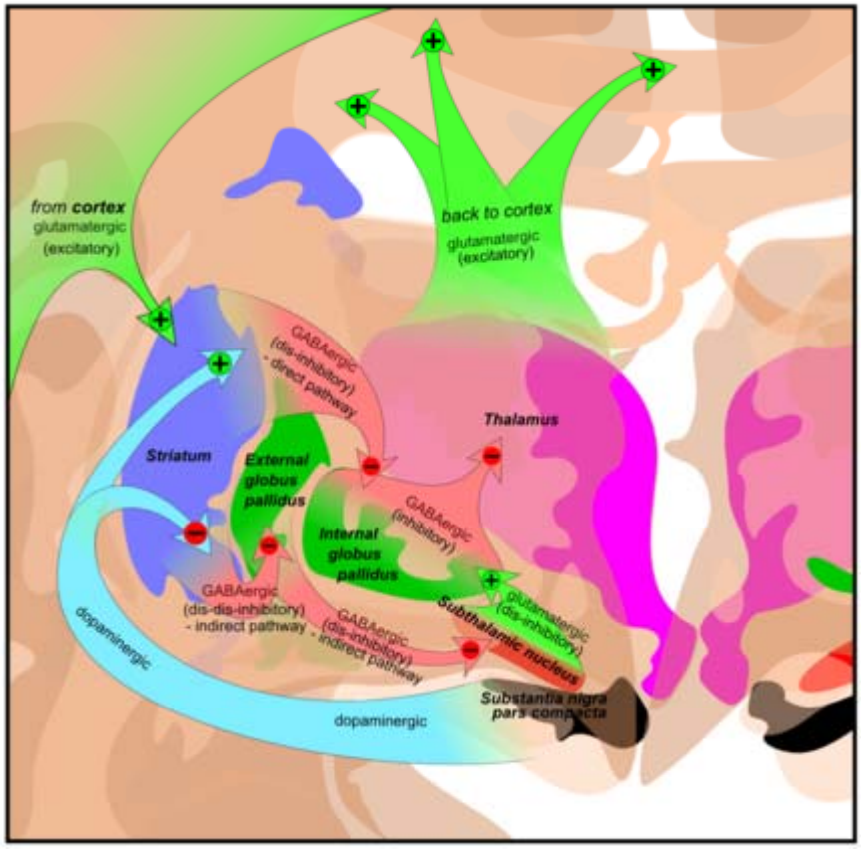
致病基因包括: SNCA、 UCH-L1、 PRKN、 LRRK2 or dardarin、 PINK1、 DJ-1 and ATP13A2。除去LRRK2基因，其余的只占致病因素的一小部分。大部分PD相关基因的研究都是SNCA和LRRK2。

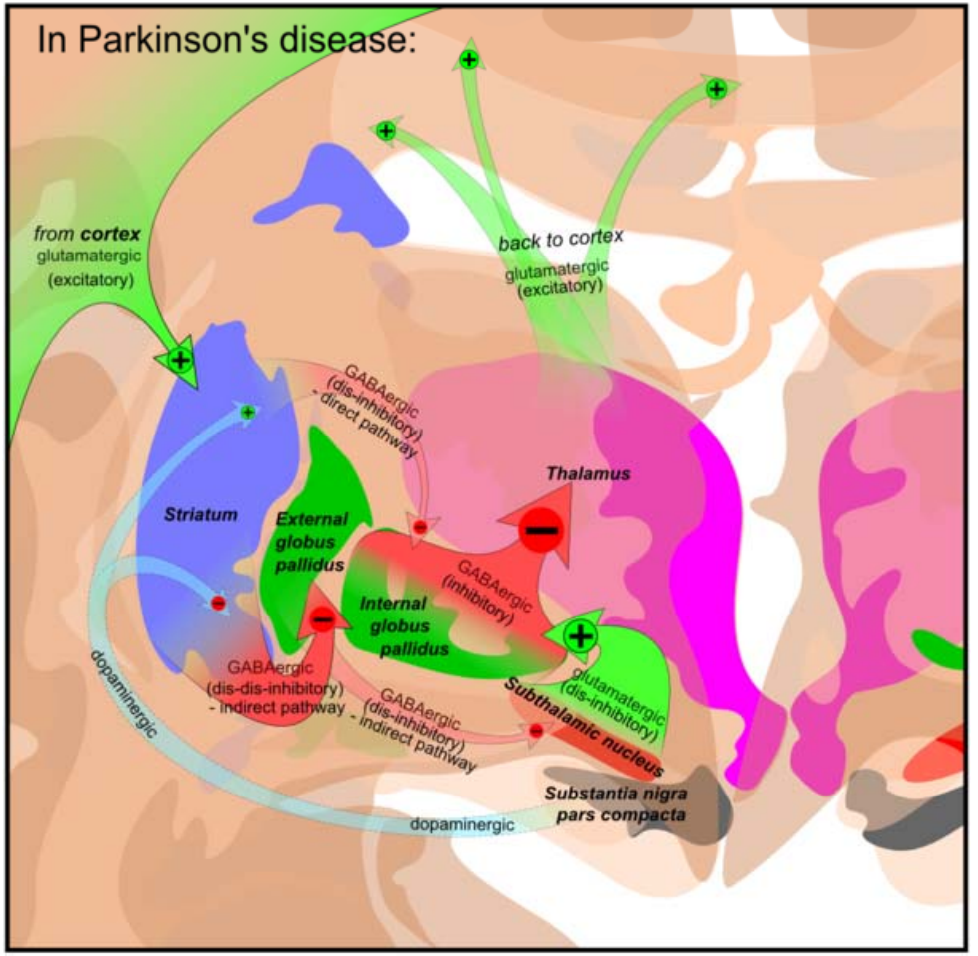
- Missense mutations of the SNCA and duplications and triplications of the locus containing it have been found in different groups with familial PD.

在不同PD家族中发现共核蛋白的错义突变以及包含该基因的位点的双倍和三倍

Pathophysiology of PD PD的病理生理学







- The main pathological characteristic of PD is cell death in the substantia nigra and more specifically the ventral part of the pars compacta, affecting up to 70% of the cells by death time. The mechanisms by which the brain cells in Parkinson's are lost are varied.

PD的主要病理特征是黑质细胞死亡，更具体地说腹侧致密部，到死亡时影响高达70%的细胞。帕金森氏症大脑细胞丢失的机制众说纷纭。

- One mechanism consists of an abnormal accumulation of the protein α-synuclein bound to ubiquitin in the damaged cells.

一种机制是在受损细胞中α -共核蛋白结合到泛素上发生异常聚集。

- Lewy bodies first appear in the olfactory bulb, medulla oblongata and pontine tegmentum, patients at this stage being asymptomatic.

路易小体首先出现在嗅球、延髓、桥脑被盖，在这个阶段病人没有症状。

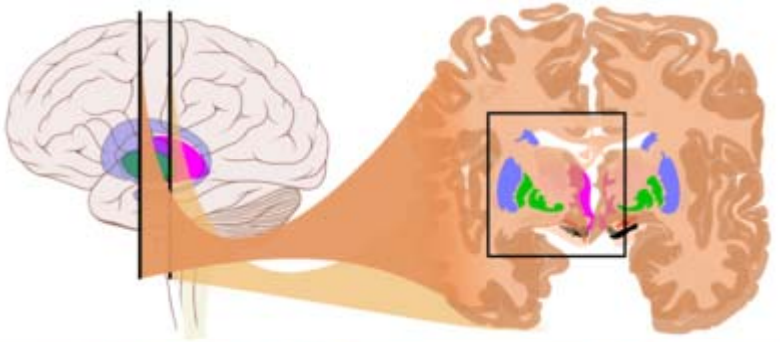
As the disease evolves, Lewy bodies later attain the substantia nigra, areas of the midbrain and basal prosencephalon and finally reach areas of the neocortex.
随着疾病的发展，路易小体随后侵占黑质、中脑和基底前脑，最终到达新皮层区域。

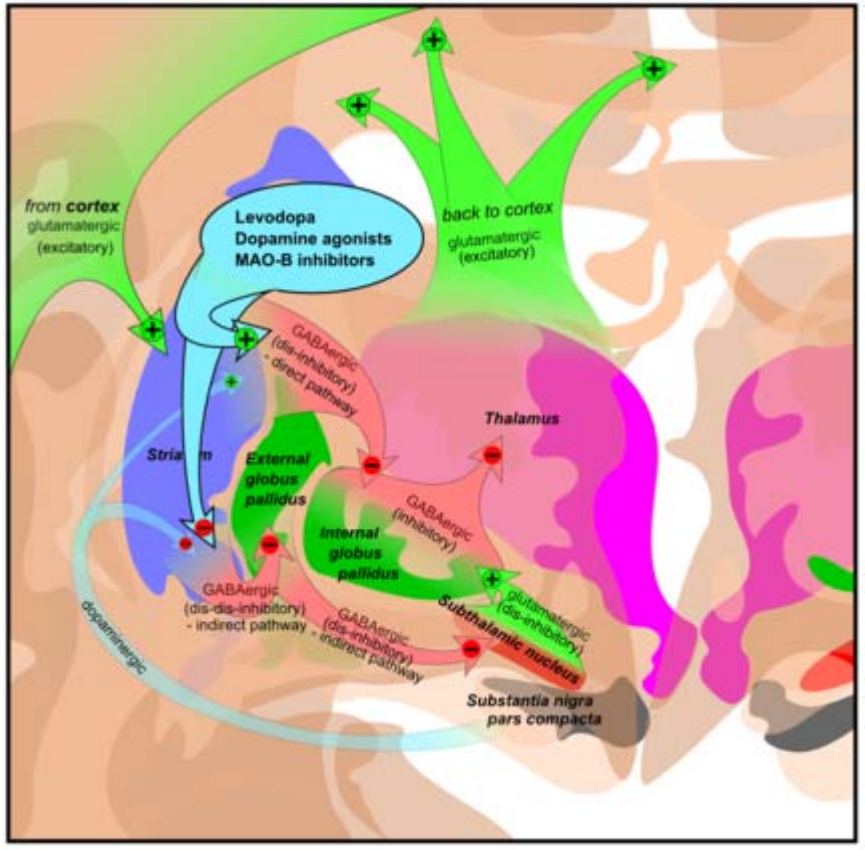
Other cell-death mechanisms include proteosomal and lysosomal system dysfunction, and reduced mitochondrial activity.
其他细胞死亡机制包括蛋白酶体和溶酶体系统功能障碍和降低的线粒体活性。

Iron accumulation in the substantia nigra of PD patients is also typically observed in conjunction with the protein inclusions.
PD患者黑质有典型铁聚集，连同蛋白质包含物一起。

It may be related to the generation of oxidative stress, protein aggregation and neuronal death, although the mechanism is not fully understood.
尽管机制不完全清楚，可能与氧化应激、蛋白质聚集和神经元死亡有关。

Levodopa 左旋多巴





- Levodopa (or L-DOPA) has been the most widely used treatment for over 30 years.

  左旋多巴作为药物治疗已有30年之久

- L-DOPA is transformed into dopamine in the dopaminergic neurons by dopa-decarboxylase. Since motor symptoms of PD are produced by a lack of dopamine in the substantia nigra, the administration of L-DOPA temporarily diminishes the motor symptomatology.

  在多巴胺能神经元中，左旋多巴在多巴脱羧酶的作用下转化为多巴胺，因为PD的运动症状是因为黑质缺少多巴胺，服用左旋多巴暂时消除了运动症状

- Only 5-10% of L-DOPA crosses the blood-brain barrier. The remaining L-DOPA is often metabolized to dopamine elsewhere, causing a wide variety of side effects including nausea, dyskinesias and stiffness.

  只有5%-10%的左旋多巴可以透过血脑屏障，剩余的左旋多巴往往在其他地方代谢为多多巴胺，产生各种各样的副作用，包括恶心、运动困难和僵直。

- Due to feedback inhibition, levodopa results in a reduction in the endogenous formation of L-DOPA, and so eventually becomes counterproductive.

由于反馈抑制，外源左旋多巴使得内源左旋多巴减少，最终达不到预期目的。

- When this occurs PD sufferers change rapidly from stages with good response to medication and few symptoms ("on" state) to phases with no response to medication and important motor symptoms ("off" state).

当这种情况发生时，PD患者的状态会由药物反应良好、症状表现较少（“开”状态）迅速变化为对药物无反应、重要运动症状显现（“关闭”状态）。

- For this reason levodopa doses are maintained as low as possible while maintaining functionality.

因此，在保持功能的同时，左旋多巴剂量尽可能维持在低水平。

Dopamine agonists 多巴胺激动剂

- Dopamine agonists in the brain have a similar effect to levodopa since they bind to dopaminergic post-synaptic receptors.

在大脑中多巴胺激动剂与左旋多巴有相似的效果，因为它们结合到多巴胺能神经元突触后受体上。

- Dopamine agonists were initially used for patients experiencing on-off fluctuations and dyskinesias as a complementary therapy to levodopa but they are now mainly used on their own as an initial therapy for motor symptoms with the aim of delaying motor complications.

多巴胺激动剂最初用在患者经历开启-关闭的波动和运动障碍时，作为左旋多巴的佐剂。但是现在他们主要用于初始治疗运动症状，以延迟运动并发症为目的。

- When used in late PD they are useful at reducing the off periods. Dopamine agonists include bromocriptine, pergolide, pramipexole, ropinirole , piribedil, cabergoline, apomorphine, and lisuride.

当使用在晚期PD时，它们对于减少“关闭”期很有效。多巴胺激动剂包括溴麦角环肽、培高利特、普拉克索、罗匹尼罗、吡贝地尔、卡麦角林、阿朴吗啡和麦角乙脲。

MAO-B inhibitors 单胺氧化酶B 抑制剂

- MAO-B inhibitors increase the level of dopamine in the basal ganglia by blocking its metabolism. They inhibit monoamine oxidase-B (MAO-B) which breaks down dopamine secreted by the dopaminergic neurons. Therefore reducing MAO-B results in higher quantities of L-DOPA in the striatum.

单胺氧化酶B抑制剂在基底神经节通过阻断其新陈代谢增加多巴胺的水平。他们抑制单胺氧化酶B的活性，该酶降解多巴胺能神经元分泌的多巴胺。因此减少单胺氧化酶B导致纹状体内左旋多巴升高。

- Similarly to dopamine agonists, MAO-B inhibitors improve motor symptoms and delay the need of taking levodopa when used as monotherapy in the first stages of the disease but produce more adverse effects and are less effective than levodopa.

类似于多巴胺激动剂，单胺氧化酶B抑制剂改善运动症状，延迟左旋多巴作为单一疗法在第一阶段的疾病的需要，但产生更多不良反应，也不如左旋多巴有效。

Gene therapy 基因治疗

- Gene therapy is currently under investigation. It involves the use of a non-infectious virus to shuttle a gene into a part of the brain. The gene used leads to the production of dopamine which helps to manage PD symptoms or protects the brain from further damage.

基因治疗现在仍在调研中。它涉及到使用一种非传染性病毒把某种基因送入脑内。该基因促使多巴胺生成，帮助控制PD症状或阻止大脑进一步受损。

- As of 2010 there are four clinical trials using gene therapy in PD. There have not been important adverse effects in these trials although the clinical usefulness of gene therapy is still unknown.

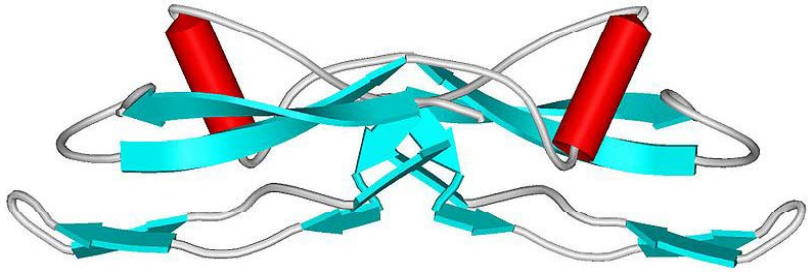
2010年以来有四个使用基因治疗PD的临床试验。这些实验暂时没有显示重大的副作用，虽然基因治疗的临床实用性仍然是未知的。

Neuroprotective treatments 神经保护治疗

- Several molecules have been proposed as potential treatments. However none of them has been conclusively demonstrated to reduce degeneration in clinical trials.

有几个分子已经被提议作为潜在的治疗方法。但是没有一个在临床试验中得出能降低退化的定论。

- Glial cell line-derived neurotrophic factor (GDNF)胶质细胞源性神经营养因子



Neural transplantation 神经移植

- Cell transplants in PD started around 1980 using very different tissues such as fetal, porcine, carotid or retinal. Although there was initial evidence of dopamine-producing cell transplants being beneficial, the best constructed studies up to date indicate that cell transplants have no effect. An additional significant problem was the excess release of dopamine by the transplanted tissue.

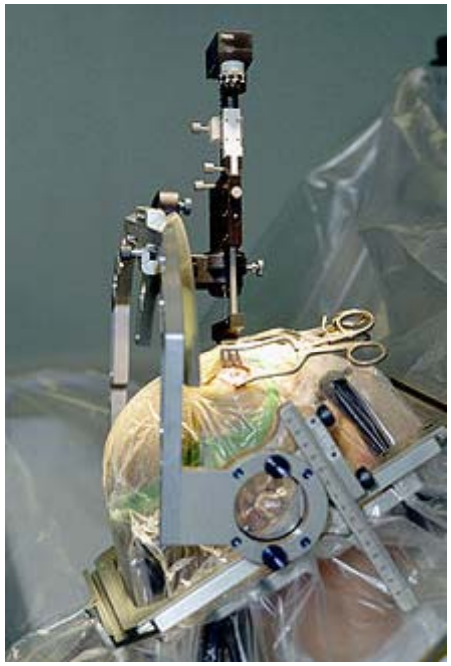
PD患者的细胞移植方案大约开始于1980年，使用不同的组织，如胎儿，猪，颈动脉或视网膜。尽管有初步的证据证明产生多巴胺的细胞移植是有益的，但最新研究表明细胞移植没有效果。另外一个严峻的问题是移植组织释放出的过多的多巴胺。

- Stem cells transplants have raised great recent interest. When transplanted into the brains of rodents and monkeys, they survive and improve behavioral abnormalities. Nevertheless while fetal stem cells are the easiest to manipulate their use is controversial. Such controversy may be overcome with the use of induced pluripotent stem cells from adults.

最近干细胞移植引起了人们的兴趣。向啮齿动物和猴子的大脑移植干细胞后，他们得以存活、行为异常得到改善。尽管胎儿干细胞最容易操作，但其使用仍有争议。这种争议也许能被成年人诱导多能干细胞的使用克服。

Deep brain stimulation 深脑刺激

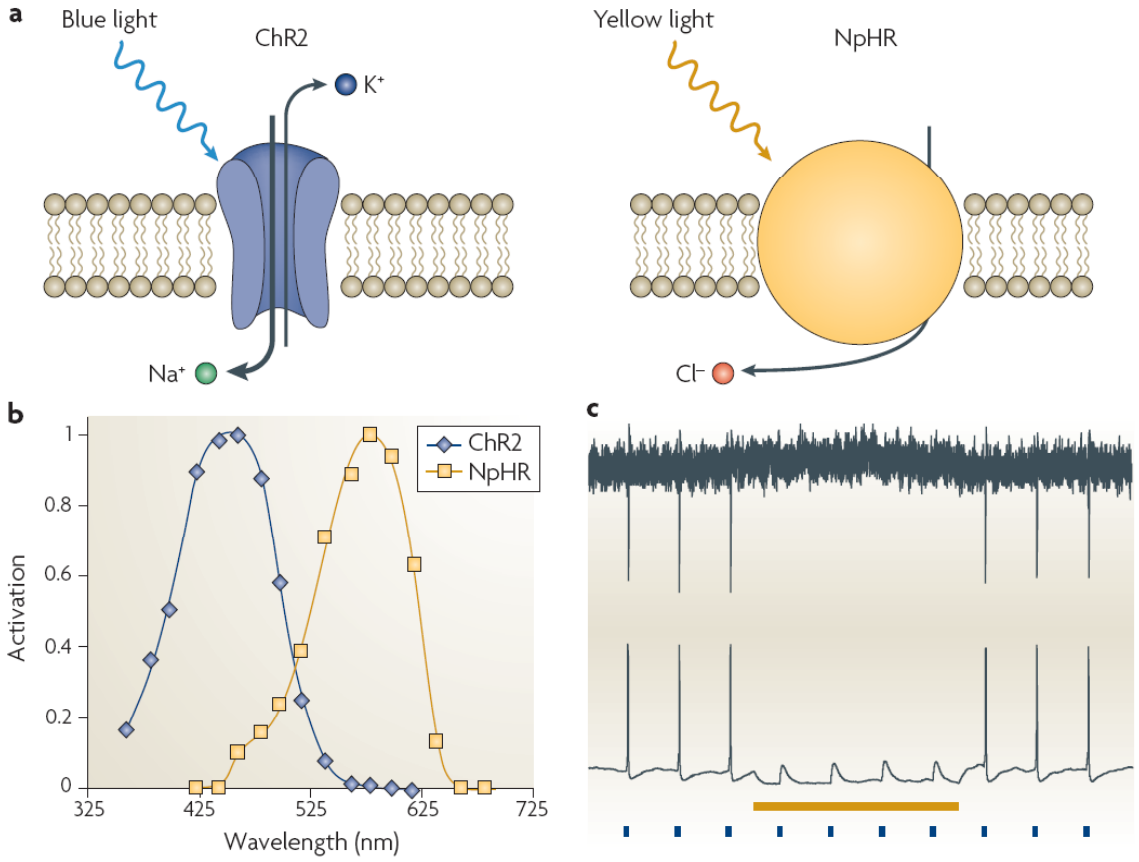
DBS is presently the most used surgical mean of treatment but other surgical therapies consisting in producing lesions in specific subcortical areas are also effective. DBS involves the implantation of a medical device called a brain pacemaker, which sends electrical impulses to specific parts of the brain. Target areas for DBS or lesions include the thalamus, the globus pallidus or the subthalamic nucleus.

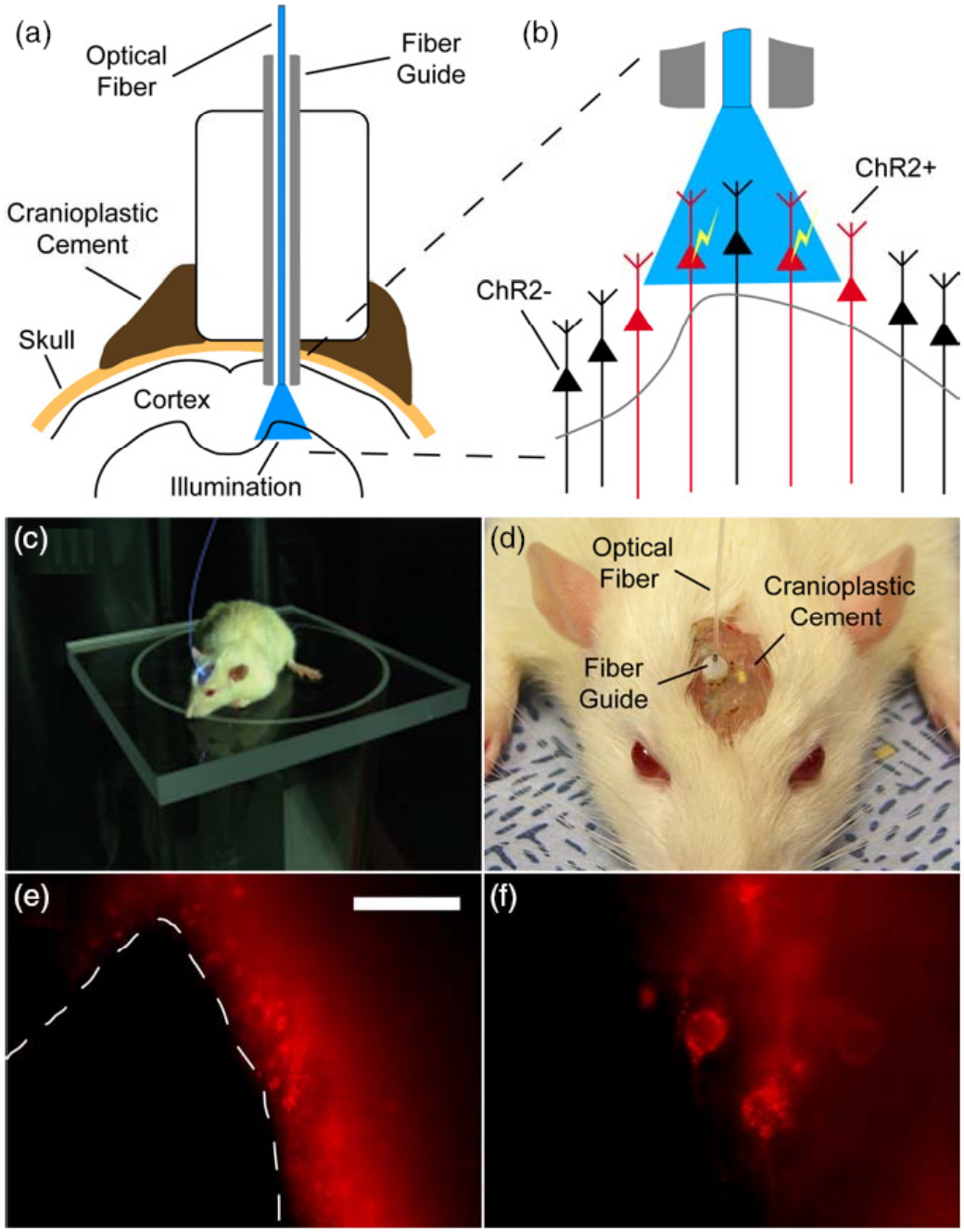


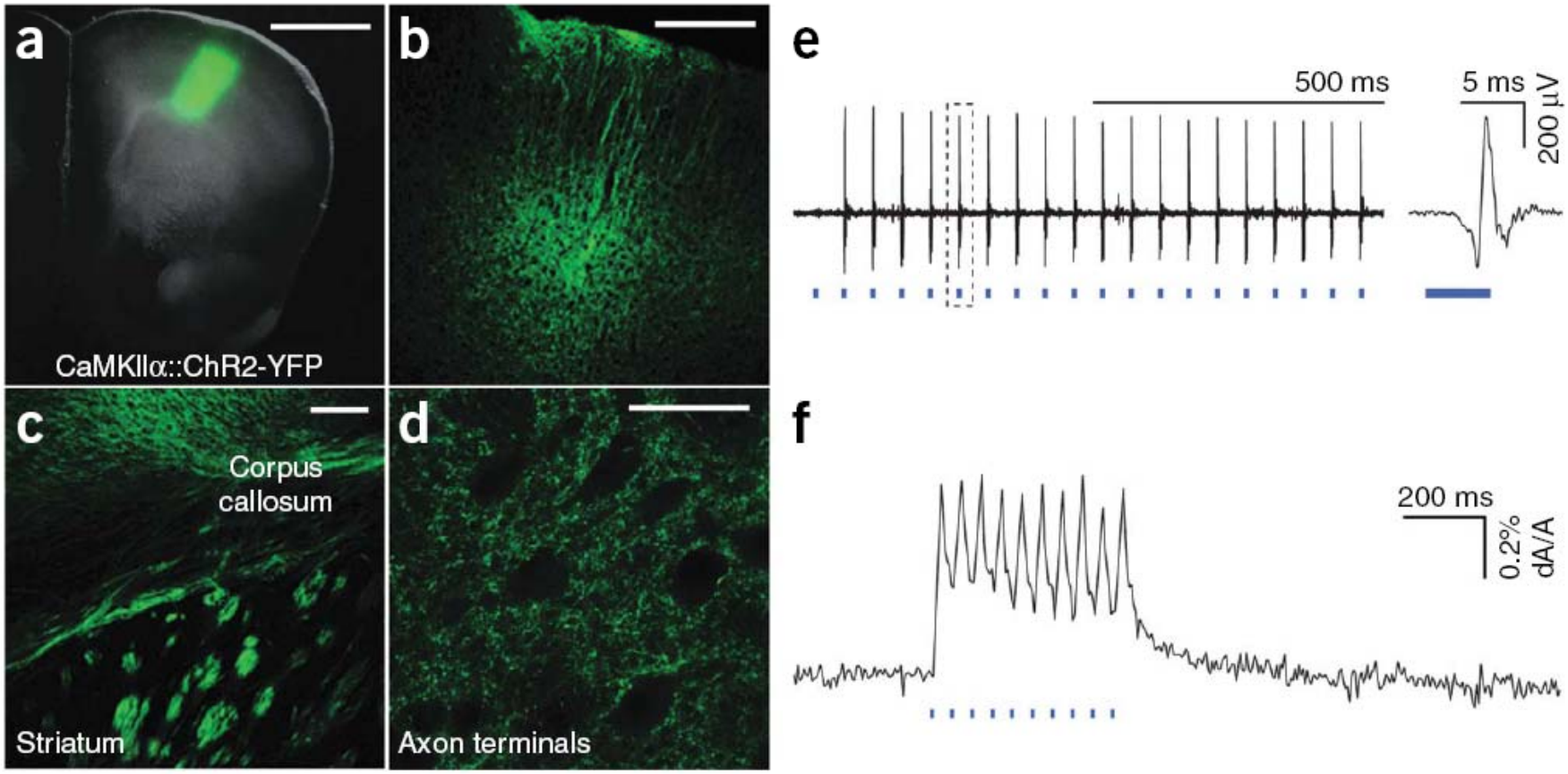
DBS是目前最常用的外科治疗，但其他损伤特定皮质下区域的手术治疗同样有效。DBS使用的医疗设备称为脑起搏器，它向大脑的特定部位发送电脉冲。DBS或损伤目标区域包括丘脑、苍白球或底丘脑核。

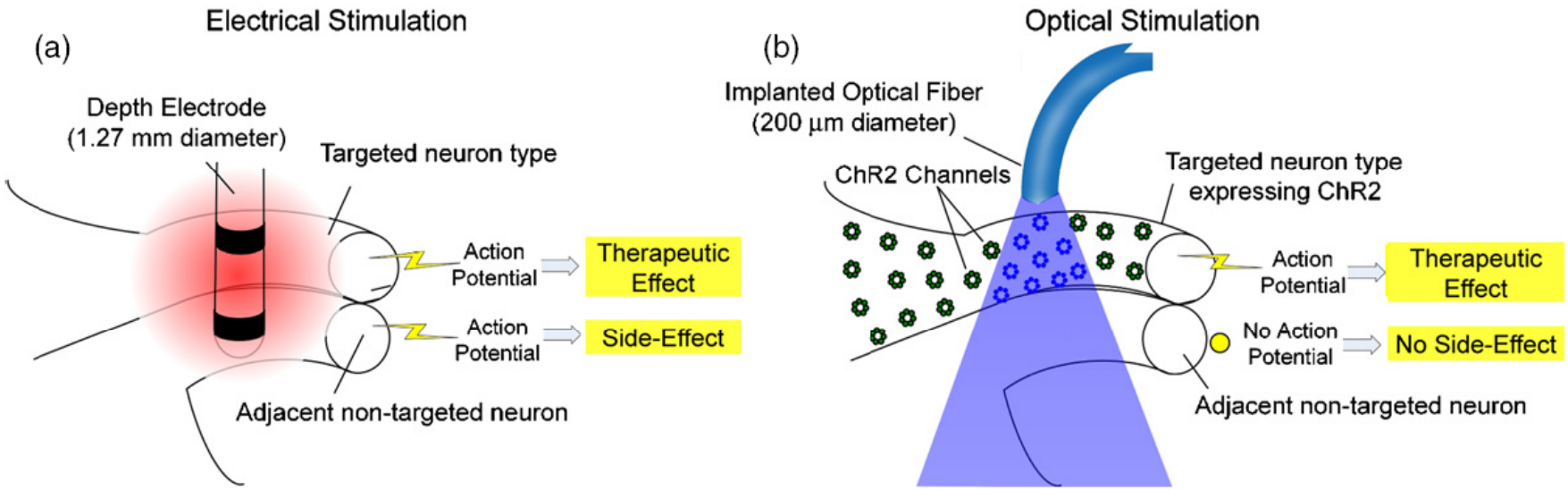
Optogenetics 光遗传学

- Developed by Dr. Karl Deisseroth at Stanford University in around 2005.
- 2005年由斯坦福大学Karl Deisseroth博士开发




(a)
Optical Fiber
Fiber Guide
Cranioplastic Cement
Skull
Cortex
Illumination
(b)
ChR2+
ChR2-
(c)
(d)
Optical Fiber
Cranioplastic Cement
Fiber Guide
(e)
(f)


a
CaMKIIα::ChR2-YFP
b
c
Corpus
callosum
Striatum
d
Axon terminals
e
500 ms
5 ms
200 µV
f
200 ms
0.2%
dA/A



- Selective, no artifact (compared to electric stimulation)

  与电刺激相比，它具有选择性，无人为因素

- Reversible (compared to drug perfusion)

  相较于药物渗透，它是可逆的

Optical Deconstruction of Parkinsonian Neural Circuitry

Viviana Gradinaru,[1,2]* Murtaza Mogri,[1]* Kimberly R. Thompson,[1]
Jaimie M. Henderson,[3] Karl Deisseroth[1,4]†

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Phasic Firing in Dopaminergic Neurons Is Sufficient for Behavioral Conditioning

Hsing-Chen Tsai,[1,2]* Feng Zhang,[2]* Antoine Adamantidis,[3] Garret D. Stuber,[4]
Antonello Bonci,[4] Luis de Lecea,[3] Karl Deisseroth[2,3]†

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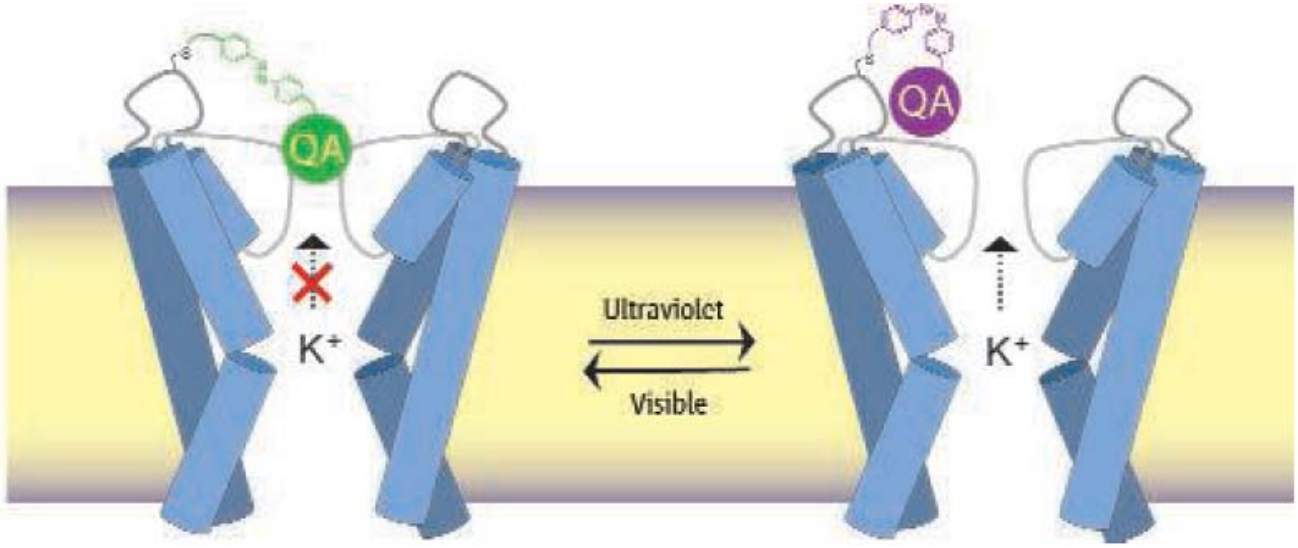
Other optogenetic systems
其他光遗传系统

- Gero Miesenbock (2005)
- Richard Kramer, Ehud Isacoff, and Dirk Trauner (2004)



Diseases caused by prions

Affected animal(s)	Disease
sheep, goat	Scrapie
cattle	Bovine spongiform encephalopathy (BSE), mad cow disease
mink	Transmissible mink encephalopathy (TME)
white-tailed deer, elk, mule deer, moose	Chronic wasting disease (CWD)
cat	Feline spongiform encephalopathy (FSE)
nyala, oryx, greater kudu	Exotic ungulate encephalopathy (EUE)
ostrich[40]	Spongiform encephalopathy (Not been shown to be transmissible.)
human	Creutzfeldt–Jakob disease (CJD)
	iatrogenic Creutzfeldt-Jakob disease (iCJD)
	variant Creutzfeldt-Jakob disease (vCJD)
	familial Creutzfeldt-Jakob disease (fCJD)
	sporadic Creutzfeldt-Jakob disease (sCJD)
	Gerstmann–Sträussler–Scheinker syndrome (GSS)
	Fatal familial insomnia (sFI)
	Kuru

Prion disease 朊病毒病

- All known prion diseases affect the structure of the brain or other neural tissue and all are currently untreatable and universally fatal.

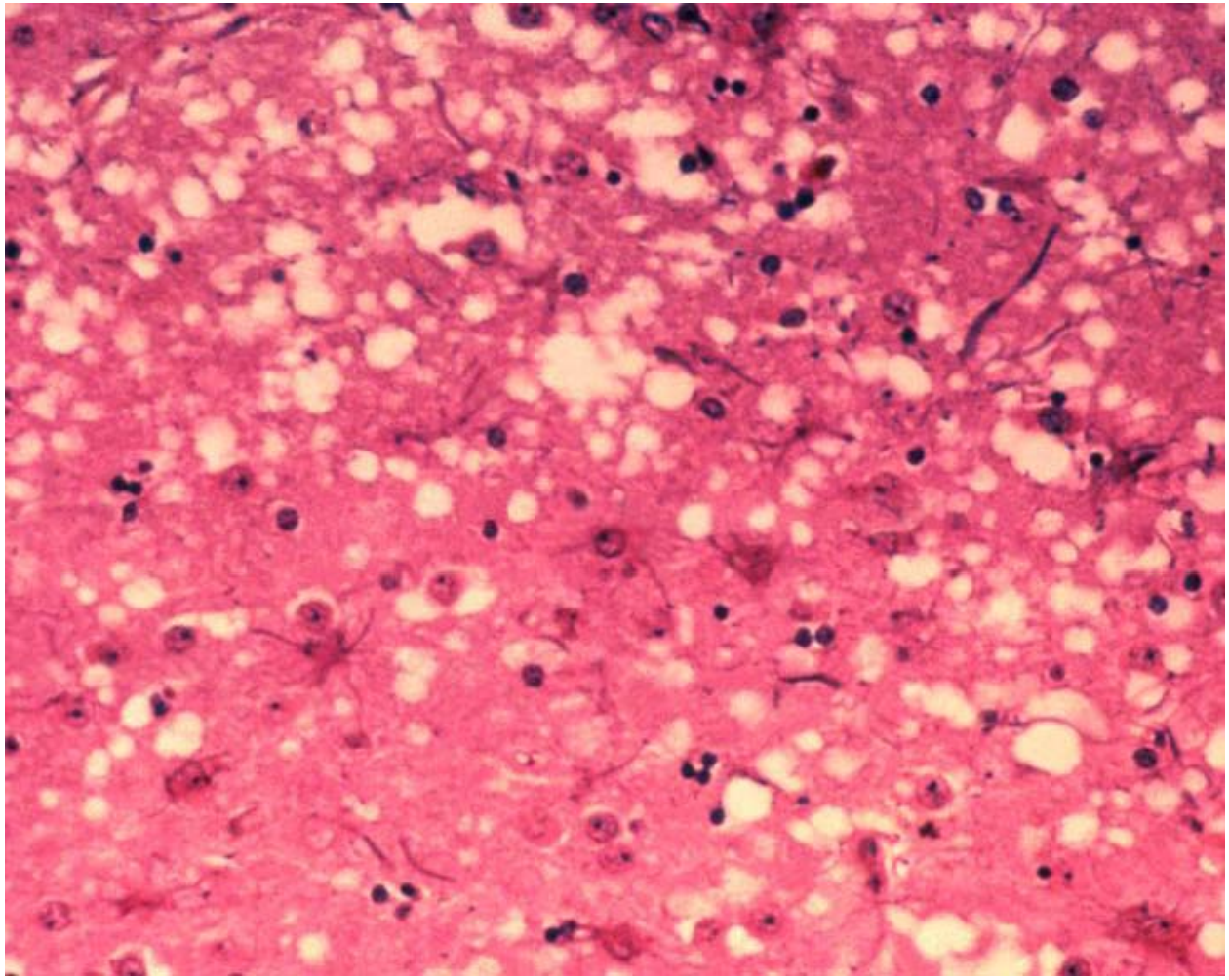
所有已知的朊病毒疾病影响大脑的结构或其他神经组织。目前无法治疗，普遍致命。

- PrP^{C} refers to the endogenous form of prion protein (PrP), which is found in a multitude of tissues, while PrP^{Sc} refers to the misfolded form of PrP.

PrP^{C}指的是内源性的朊蛋白(PrP)，在大量组织中均有发现，而PrP^{Sc}指PrP的错误折叠形式。

Prion: proteinaceous infectious particle

朊病毒:蛋白质侵染粒子



Discovery of prion 朊病毒的发现

- Radiation biologist Tikvah Alper and mathematician John Stanley Griffith developed the hypothesis during the 1960s that some transmissible spongiform encephalopathies are caused by an infectious agent consisting solely of proteins.

20世纪60年代，辐射生物学家 Tikvah Alper 和数学家John Stanley Griffith 提出假说：一些传染性海绵状脑病仅由蛋白质致病因子引起。

- Their theory was developed to explain the discovery that the mysterious infectious agent causing the diseases scrapie and CJD resisted ionizing radiation.

他们的理论可以解释为什么羊瘙痒症和克雅氏症的神秘致病因子耐电离辐射

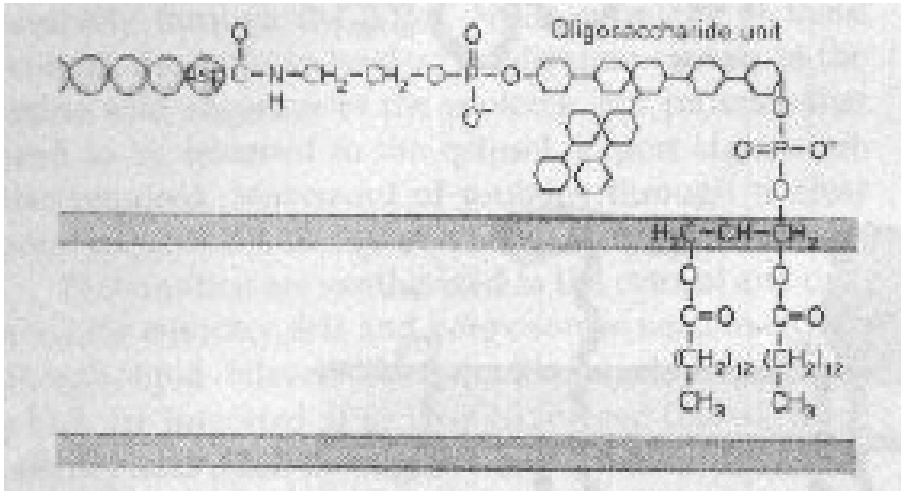
- Francis Crick recognized the potential importance of the protein-only hypothesis for scrapie propagation in the second edition of his "Central dogma of molecular biology": while asserting that the flow of sequence information from protein to protein, or from protein to RNA and DNA was "precluded". He noted that Griffith's hypothesis was a potential contradiction.

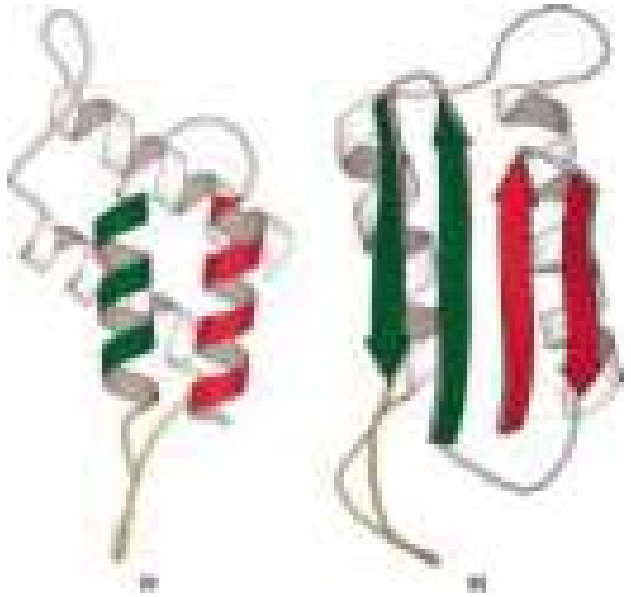
Francis Crick意识到通过痒病传播提出的“蛋白可遗传”假说在他第二版的“分子生物学的中心法则”有潜在重要性：虽然声称从蛋白质到蛋白质序列信息的流动、或从蛋白质到RNA和DNA是“排斥”的。他指出格里菲斯的假说存在一个潜在的矛盾。

- Stanley Prusiner (UCSF) announced in 1982 that his team had purified the hypothetical infectious prion, and that the infectious agent consisted mainly of a specific protein – though they did not manage to isolate the protein until two years after Prusiner's announcement. Prusiner coined the word "prion" as a name for the infectious agent. While the infectious agent was named a prion, the specific protein that the prion was composed of is also known as the **Pr**ion **P**rotein (PrP), though this protein may occur both in infectious and non-infectious forms. Prusiner was awarded the Nobel Prize in Physiology or Medicine in 1997 for his research into prions.

1982年，旧金山加州大学的Stanley Prusiner教授在宣布他的团队纯化出了理论上的传染性朊病毒，而且致病因子主要仅由一个特定蛋白构成，尽管他们两年后才分离成功。Prusiner创造了“朊病毒”一词作为致病因子的名字。尽管致病因子被命名为朊病毒，朊病毒的特定蛋白质也被称为朊蛋白(PrP)，不过这种蛋白质兼有传染性和非传染性两种形式。Prusiner因此被授予1997年诺贝尔生理学或医学奖。

GPI anchored protein GPI锚定蛋白





Protein hypothesis 蛋白假说

- The "protein hypothesis" states that a protein structure can replicate without the use of nucleic acid. This was initially controversial as it contradicts the so-called "central dogma of molecular biology", which describes nucleic acid as the central form of replicative information.

“蛋白假说”：一种蛋白质结构可自行复制，无需核酸参与。这最初是有争议的，因为它有悖于以核酸为中心复制信息的“分子生物学中心法则”。

Evidence for protein hypothesis
蛋白假说的依据

- No virus particles, bacteria, or fungi have been conclusively associated with prion diseases.

  没有与朊病毒病相关的病毒颗粒、细菌或真菌
- No nucleic acid has been conclusively associated with infectivity.

  没有与传染性相关的核酸参与
- No immune response to infection.

  没有免疫反应
- Familial prion disease occurs in families with a mutation in the PrP gene, and mice with PrP mutations develop prion disease despite controlled conditions where transmission is prevented.

  家族性朊病毒疾病由PrP基因的突变造成。尽管传播条件受控，PrP突变的小鼠仍患有朊病毒疾病。

- Animals lacking PrP^C do not contract prion disease.

PrP^C缺失的动物不感染朊病毒病

- Infectious prions can be formed *de novo* from purified non-infectious components, in the absence of gene-coding nucleic acids.

在缺乏编码核酸的情况下，传染性的朊病毒可由纯化的非传染性组分形成

Multi-component hypothesis
多组分假说

- In 2007, Surachai Supattapone produced purified infectious prions *de novo* from defined components (PrP^C, co-purified lipids, and a synthetic polyanionic molecule), leading them to hypothesize that infectious prions may be composed of multiple host components, including PrP, lipid, and polyanionic molecules, rather than PrP^{Sc} alone.

2007年,Surachai Supattapone重新从明确的成分(PrP^C、共纯化脂质和合成多阴离子分子)纯化出感染性朊病毒，他们因此假设感染性朊病毒可能由多个组分构成，包括PrP、脂质、阴离子，而不是只有朊蛋白。

- In 2010, Jiyan Ma and colleagues at The Ohio State University produced infectious prions from a recipe of bacterially expressed recombinant PrP, phospholipid, and RNA, further supporting the multi-component hypothesis. This finding is in contrast to studies that found minimal infectious prions produced from recombinant PrP alone.

2010年,俄亥俄州立大学的Jiyan Ma和同事从细菌表达的重组PrP、磷脂和RNA中得到感染性朊病毒，进一步支持多组分假设。这一发现与重组PrP得来的最少量感染性朊病毒的发现相矛盾。

Heavy metal poisoning hypothesis

重金属中毒假说

- Recent reports suggest that imbalance of brain metal homeostasis is a significant cause of PrP^{Sc}-associated neurotoxicity, though the underlying mechanisms are difficult to explain based on existing information.

最近的报告表明，大脑内金属内稳态的不平衡是导致PrPSc相关神经毒性的重要原因，尽管基于已有信息其潜在机制难以解释。

- Proposed hypotheses include a functional role for PrP^{C} in metal metabolism, and loss of this function due to aggregation to the disease associated PrP^{Sc} form as the cause of brain metal imbalance.

假说包括PrP^{C}在金属新陈代谢中发挥的功能，由于疾病相关的PrPSc导致脑内金属失衡，使该功能损失。

- Other views suggest gain of toxic function by PrP^{Sc} due to sequestration of PrP^{C}-associated metals within the aggregates, resulting in the generation of redox-active PrP^{Sc} complexes. The physiological implications of some PrP^{C}-metal interactions are known, while others are still unclear. The pathological implications of PrP^{C}-metal interaction include metal-induced oxidative damage, and in some instances conversion of PrP^{C} to a PrP^{Sc}-like form.

其他解释PrP^{Sc}毒性的观点表示，由于PrP^{C}螯合的金属离子在聚合物内聚集，导致氧化还原态的PrP^{Sc}复合体生成。一些PrP^{C}金属相互作用的生理功能已经知道，其他的还不清楚。PrP^{C}与金属相互作用的病理包括：金属引起的氧化损伤，以及在某些情况下PrP^{C}向类PrP^{Sc}的转化。

Viral hypothesis 病毒假说

- For more than a decade, Yale University neuropathologist Laura Manuelidis has been proposing that prion diseases are caused instead by an unidentified "slow" virus.

十多年来，耶鲁大学神经病理学家Laura Manuelidis提议朊病毒疾病一个身份不明的“慢”病毒造成

- In January 2007, she and her colleagues published an article reporting to have found a virus in 10%, or less, of their scrapie-infected cells in culture.

2007年1月,她和她的同事发表了一篇文章报告在培养的感染痒病细胞中，发现了10%或者更少的病毒。

- The virion hypothesis states that TSEs are caused by a replicable informational molecule (which is likely to be a nucleic acid) bound to PrP. Many TSEs, including scrapie and BSE, show strains with specific and distinct biological properties, a feature which supporters of the virion hypothesis feel is not explained by prions.

病毒粒子假说认为传染性海绵状脑病是由一个结合到PrP上的可复制的信息分子(这可能是一个核酸) 造成的。许多的传染性海绵状脑病，包括痒病和疯牛病，有特定的不同的生物学特质，使得病毒粒子假说的支持者认为不能由朊病毒解释。

- Strain variation: differences in prion infectivity, incubation, symptomology and progression among species resembles that seen between viruses, especially RNA viruses.

品系差异：朊病毒传染性、潜伏、症候学和进程的种间差异类似于病毒尤其是RNA病毒

- The long incubation and rapid onset of symptoms resembles lentiviruses, such as HIV-induced AIDS.

漫长的潜伏期和迅速的发病慢病毒类似，如HIV病毒导致的艾滋病。

- Viral-like particles that do not appear to be composed of PrP have been found in some of the cells of scrapie- or CJD-infected cell lines.

在一些痒病或克雅式症感染的细胞株发现了看起来不是由PrP组成的病毒样颗粒。

Recent studies propagating TSE infectivity in cell-free reactions and in purified component chemical reactions strongly suggest against TSE viral nature.

最近在无细胞反应和纯化成分化学反应中对海绵状脑病传染性的研究强烈反对其病毒属性。

Prion protein 朊病毒蛋白

- Found throughout the body, even in healthy people and animals.

遍布全身，即使是健康的人和动物

- PrP^C is readily digested by proteinase K and can be liberated from the cell surface in vitro by the enzyme phosphoinositide phospholipase C (PI-PLC), which cleaves the GPI glycolipid anchor.

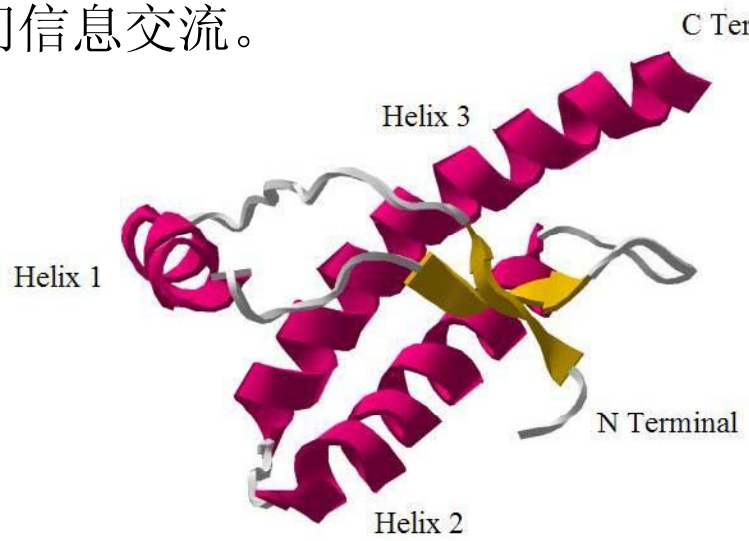
PrP^C容易通过蛋白酶K消化，在体外，酶磷酸肌醇磷脂酶C(PI-PLC) 剪切GPI糖脂锚，使得PrP^C从细胞表面释放。

- Its function is a complex issue that continues to be investigated.

它的功能是一个仍在探索的复杂的问题

- PrP has been reported to play important roles in cell-cell adhesion and intracellular signaling *in vivo*, and may therefore be involved in cell-cell communication in the brain.

据报道， PrP在体内细胞间粘附和信号传递起着重要的作用，因此可能在大脑中参与细胞间信息交流。



PrP function PrP的功能

- It has been proposed that neurodegeneration caused by prions may be related to abnormal function of PrP. However, the physiological function of the prion protein remains a controversial matter.

有人认为朊病毒引起的神经退行性疾病可能与PrP功能异常有关。然而，朊蛋白的生理功能仍有争议

- While data from in vitro experiments suggest many dissimilar roles, studies on PrP knockout mice have provided only limited information because these animals exhibit only minor abnormalities. In recent research done in mice, it was found that the cleavage of prions in peripheral nerves causes the activation of myelin repair in Schwann cells and that the lack of prions caused demyelination in those cells.

虽然体外实验数据揭示了许多不同的作用，对PrP基因敲除小鼠的研究只提供了有限的信息，因为这些动物只表现出轻微的异常。最近小鼠实验发现周围神经系统中朊病毒的剪切激活施旺细胞髓鞘修复，缺乏朊病毒导致这些细胞脱髓鞘。

- There is evidence that PrP may have a normal function in maintenance of long-term memory. Maglio and colleagues have shown that mice without the genes for normal cellular PrP protein have altered hippocampal LTP.

有证据表明，PrP可能维护长期记忆的正常功能。Maglio和他的同事们已经表明，没有合成正常PrP蛋白基因的小鼠，他们海马的LTP受到改变。

- A 2006 article from the Whitehead Institute for Biomedical Research indicates that PrP expression on stem cells is necessary for an organism's self-renewal of bone marrow. The study showed that all long-term hematopoietic stem cells expressed PrP on their cell membrane.

怀特黑德生物医学研究所2006年的一篇文章表明，干细胞中PrP的表达对于机体骨髓的自我更新是必要的。研究表明所有长期造血干细胞细胞膜上均表达PrP。

PrP^{SC}

- The infectious form of PrP, is able to convert normal PrP^{C} proteins into the infectious isoform by changing their conformation or shape; this, in turn, alters the way the proteins interconnect.

传染形式的PrP可以把PrP^{C}构象或形状转变为传染性亚型，因此改变了蛋白质间的相互联系。

- Although the exact 3D structure of PrP^{Sc} is not known, it has a higher proportion of β-sheet structure in place of the normal α-helix structure. Aggregations of these abnormal isoforms form highly structured fibers, which accumulate to form plaques.

尽管PrP^{Sc}的确切三维结构是未知的,它有一个更高比例的β片层来代替正常的α螺旋。这些异常亚型的聚集形成高度结构化的纤维，它们积累形成斑块。

It is unclear if these aggregates are the cause of cell damage or are simply a side effect of the underlying disease process. The end of each fiber acts as a template onto which free protein molecules may attach, allowing the fiber to grow. Only PrP molecules with an identical amino acid sequence to the infectious PrP^{Sc} are incorporated into the growing fiber.

目前还不清楚这些聚集引起细胞损伤，或者仅仅是一个潜在疾病过程的副作用。每个纤维的末端都可以被自由蛋白质分子附着，使纤维生长。只有与传染性PrP^{Sc}的具有相同的氨基酸序列的PrP分子可以并入生长纤维中。

Prion replication mechanism

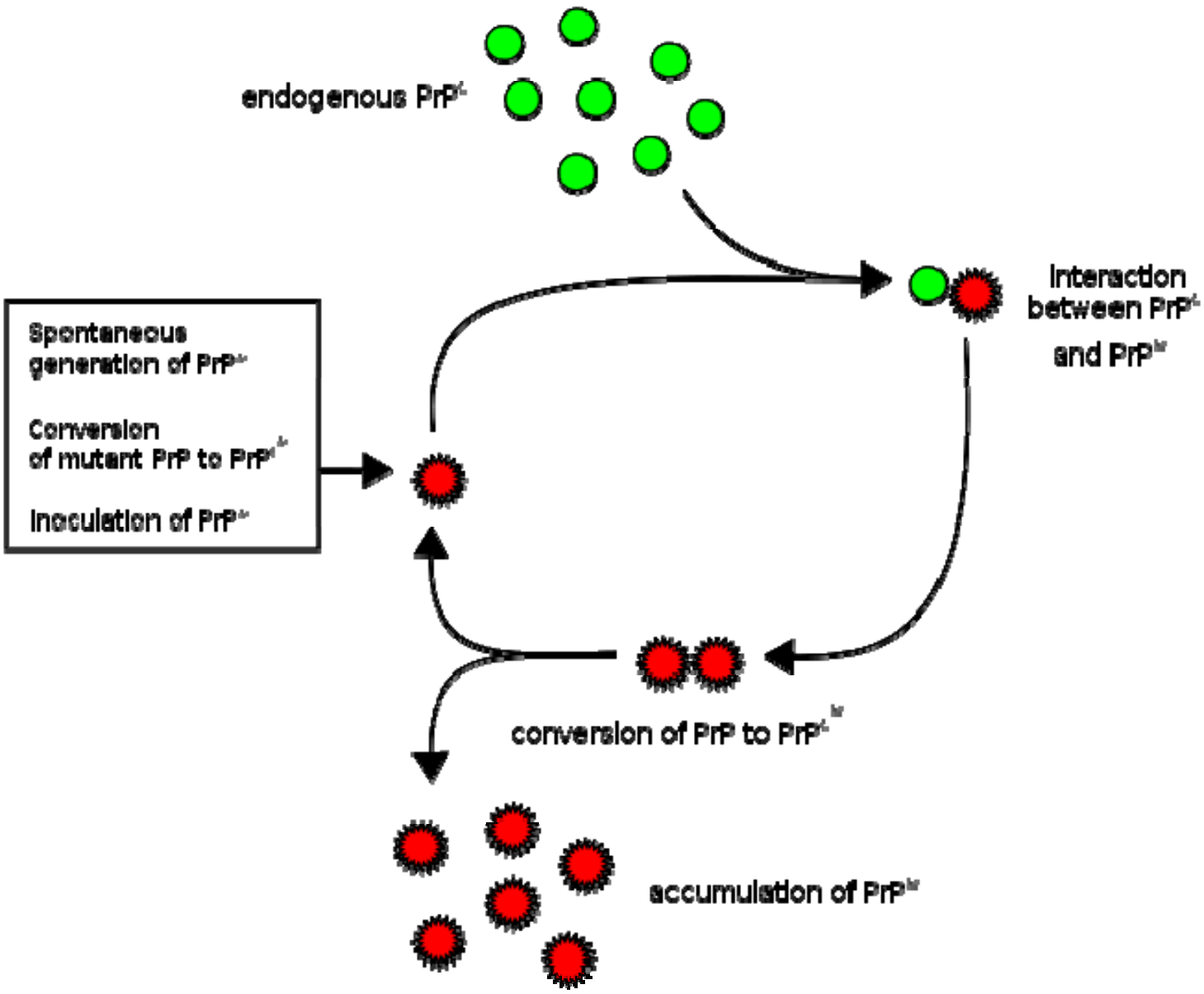
朊病毒的复制机制

- **Heterodimer model:** This model assumed that a single PrP^{Sc} molecule binds to a single PrP^{C} molecule and catalyzes its conversion into PrP^{Sc}. The two PrP^{Sc} molecules then come apart and can go on to convert more PrP^{C}. However, since PrP^{C} has a very low rate of spontaneous conversion into PrP^{Sc}, the heterodimer model requires PrP^{Sc} to be an extraordinarily effective catalyst, increasing the rate of the conversion reaction by a factor of around 10^{15}. What is more, despite considerable effort, infectious monomeric PrP^{Sc} has never been isolated. Theory and experiments both suggest that PrP^{Sc} exists only in aggregated forms.

异二聚体模型：该模型假定一个PrP^{Sc}分子结合到一个PrP^{C}分子，催化后者转化成PrP^{Sc}。随后两个朊蛋白分子分开，可以转化更多的PrP^{C}。然而，由于PrP^{C}自发转化成PrP^{Sc}的效率很低，异二聚体模型要求PrP^{Sc}作为非常有效的催化剂，使转换反应的速率增加约10^{15}倍。另外，尽管付出相当大的努力，传染性单体PrP^{Sc}一直没有被成功分离出来。理论和实验都表明PrP^{Sc}只以聚合体形式存在。

- An alternative model assumes that PrP^{Sc} exists only as fibrils, and that fibril ends bind PrP^{C} and convert it into PrP^{Sc}. If this were all, then the quantity of prions would increase linearly, forming ever longer fibrils. But exponential growth of both PrP^{Sc} and of the quantity of infectious particles is observed during prion disease. This can be explained by taking into account fibril breakage. The incubation period is determined by the exponential growth rate, and in vivo data on prion diseases in transgenic mice match this prediction.

另一种模型假定PrPSc只作为纤维存在，末端结合PrP^{C}并将之转化成朊蛋白。假定如此，那么朊病毒的数量将线性增加，形成长纤维。但在朊病毒疾病中观察到的PrP^{Sc}和传染性微粒的数量都是呈指数增长的。将纤维断裂考虑进去就可以解释通了。潜伏期是由指数增长率决定的，转基因老鼠朊病毒疾病的在体数据和这个预测吻合。


endogenous PrP^c
Interaction between PrP^c and PrP^sc
Spontaneous generation of PrP^sc
Conversion of mutant PrP to PrP^c
Inoculation of PrP^sc
conversion of PrP to PrP^sc
accumulation of PrP^sc

Genetic factors 遗传因素

- A gene for the normal protein has been identified: the *PRNP* gene. In all inherited cases of prion disease, there is a mutation in the *PRNP* gene.

一个正常的蛋白质基因已被确认:PRNP基因。在所有的遗传病例中都有一个PRNP基因突变。

- Many different *PRNP* mutations have been identified and it is thought that the mutations somehow make PrP^{C} more likely to change spontaneously into the abnormal PrP^{Sc} form. Although this discovery puts a hole in the general prion hypothesis, that prions can only aggregate proteins of identical amino acid make up.

许多不同PRNP基因突变已经得到鉴定，并被并认为以某种方式使PrP^{C}更有可能自发转化成异常PrP^{Sc}。虽然这个发现使朊病毒假说出现漏洞，朊病毒只聚集氨基酸组成相同的蛋白质这一点依然可以成立。

- These mutations can occur throughout the gene. Some mutations involve expansion of the octapeptide repeat region at the N-terminal of PrP.

这些突变可以发生在整个基因。一些突变涉及PrP的N端八肽重复区域的扩张。

- Other mutations that have been identified as a cause of inherited prion disease occur at positions 102, 117 & 198 (GSS), 200, 210 & 232 (CJD) and 178 (Fatal Familial Insomnia, FFI).

其他突变被确认为遗传性朊病毒疾病发生的一个原因在第102、117、198位(GSS)，200、210和232位(克雅氏症)和178位(致死性家族性失眠症，FFI)。

- The cause of prion disease can be sporadic, genetic and infectious, or a combination of these factors. For example, in order to have scrapie, both an infectious agent and a susceptible genotype need to be present.

朊病毒疾病的原因可能是分散的、遗传性的和感染性的，或这些因素的结合。例如，在痒病中，致病因子和易感基因型都要存在。

Sterilization 灭活

- Prions are infectious by their effect on normal versions of the protein. Sterilizing prions therefore involves the denaturation of the protein to a state where the molecule is no longer able to induce the abnormal folding of normal proteins.

朊病毒通过影响正常的蛋白质导致传染。消毒因此涉及蛋白质的变性，使得该分子不再能够诱导正常蛋白质的异常折叠。

- Prions are generally quite resistant to proteases, heat, radiation, and formalin treatments, although their infectivity can be reduced by such treatments. Effective prion decontamination relies upon protein hydrolysis or reduction or destruction of protein tertiary structure.

朊病毒通常耐蛋白酶、热、辐射和福尔马林处理，尽管传染性会降低。有效的朊病毒净化依赖蛋白质水解、减少或蛋白质三级结构的破坏。

- 134°C (274°F) for 18 minutes in a pressurized steam autoclave may not be enough to deactivate the agent of disease.

加压蒸汽高压灭菌器，134°C (274°F)，18分钟可能不足以使致病因子失活。

- Ozone sterilization is currently being studied as a potential method for prion denature and deactivation.

臭氧杀菌作为潜在的朊病毒变性和失活方法尚在研究中

- Renaturation of a completely denatured prion to infectious status has not yet been achieved, however partially denatured prions can be renatured to an infective status under certain artificial conditions.

尚未实现把完全变性的朊病毒复性到感染状态，然而在某些人工条件下，部分变性朊病毒可以复性到感染状态。

WHO suggested protocol
世界卫生组织建议的步骤

- Immerse in a pan containing 1N NaOH and heat in a gravity-displacement autoclave at 121° C for 30 minutes; clean; rinse in water.

  浸入1当量浓度NaOH中，在重力置换高压灭菌锅中加热至121° C，维持30 分钟，清洁，用水冲洗。
- Immerse in 1N NaOH or sodium hypocholorite (20,000 parts per million available chlorine) for 1 hour; transfer instruments to water; heat in a gravity-displacement autoclave at 121° C for 1 hour; clean.

  浸入1当量浓度NaOH或NaClO（每100万有效氯中的2万份）中1小时，放入水中，在重力置换高压灭菌锅中加热至121° C，维持30分钟，清洁。
- Immerse in 1N NaOH or sodium hypochlorite (20,000 parts per million available chlorine) for 1 hour; remove and rinse in water, then transfer to an open pan and heat in a gravity-displacement (121° C) or in a porous-load (134° C) autoclave for 1 hour; clean; and then perform routine sterilization processes.
- 浸入1当量浓度NaOH或NaClO（每100万有效氯中的2万份）中1小时，放入水中，转移至开口容器中，在重力置换高压灭菌锅中加热至121° C或在透气高压灭菌锅中加热至134° C，维持1小时，清洁，进行日常消毒。