findings. Li *et al.*[6] further showed that presenilin 1 is first synthesized as a zymogen (an inactive precursor protease), which does not bind the inhibitor, and becomes active only when it is cleaved into amino- and carboxy-terminal fragments[14]. Both fragments appear to contribute to the active site of presenilin because, depending on the orientation of the crosslinking moiety, the inhibitor binds to either of them[6]. This finding is consistent with the model proposed by Wolfe *et al.*[13], because each fragment contributes one aspartate to the putative active site of γ-secretase (Fig. 1). So we now have compelling evidence that presenilins are examples of a new class of aspartyl proteases.

Is research into presenilin and γ-secretase now at an end? Certainly not, and much more work will be needed before we really understand how hydrolysis of peptide bonds in the hydrophobic cell membrane can occur. The possibility that the transmembrane domains of presenilin provide a hydrophilic pocket, allowing water to enter the catalytic site, needs further scrutiny. The identity and role of other proteins, thought by many investigators to be associated with the presenilins in a multiprotein complex, also needs clarification. The putative catalytic site of presenilin is especially intriguing because it is completely divergent from the consensus site of classical aspartyl proteases.

The development of clinically useful γ-secretase inhibitors is likely to be long and tedious. One hurdle will be the delivery of such drugs to neurons in the brain. For instance, the inhibitors used by Li *et al.*[6] and Esler *et al.*[7] do not cross cell membranes efficiently, and will probably be of little use *in vivo*. The good news is that pharmaceutical companies now have another defined target for their drug-discovery machineries.

The insights of the current studies go beyond research into Alzheimer's disease and are highly relevant to cell biology. The presenilins are only the second class of eukaryotic proteases found to be involved in regulated intramembrane proteolysis — a process that causes the proteolytic release of the cytoplasmic domain of integral membrane proteins. These proteins then migrate to the nucleus to activate the transcription of genes that are pivotal in cellular differentiation, the unfolded-protein stress response and cholesterol biosynthesis[15]. Presenilin is apparently involved not only in APP processing, but also in regulated intramembrane proteolysis of the Notch receptor, which is a central player in development, and probably of the Ire1 protein, which controls the unfolded-protein stress response[9,15]. All in all, there remains much to do — in particular, the hunt is now on for other substrates of presenilin, alias γ-secretase, and for proteins that regulate its activity. ■

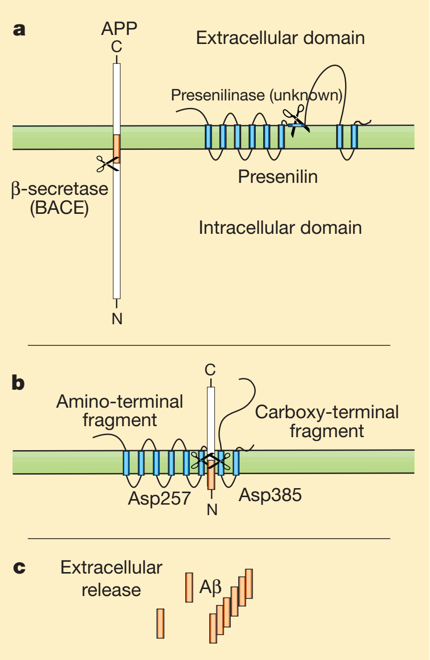

Figure 1 **Generation of the amyloid peptide Aβ.** a, **Amyloid precursor protein (APP) is first cleaved by β-secretase, which releases its extracellular domain. Presenilin is processed shortly after its biosynthesis by an unknown protease, called presenilinase, to yield amino-terminal and carboxy-terminal fragments.** b, **These fragments remain non-covalently associated and form the active γ-secretase. Each fragment contributes one aspartyl residue (Asp 257 or Asp 385) to the active site. The β-secretase-cleaved APP fragment associates with and becomes cleaved by presenilin in an unidentified subcellular compartment.** c, **This results in the release of Aβ (orange) in the extracellular 'milieu'. Aβ then aggregates into the amyloid plaques observed in the brain of patients suffering from Alzheimer's disease.**

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Semiconductor physics

Half-matter, half-light amplifier

Yoshihisa Yamamoto

A small semiconductor chip generating coherent light waves is commonplace in modern life, from global telecommunication networks to personal compact disk players. This semiconductor light-emitting device is based on the principle of 'light amplification by stimulated emission of radiation' (laser). Quantum mechanically, matter can also be regarded as waves. There are two fundamental types of particle that can make matter waves: bosons and fermions. As a consequence of the Pauli exclusion principle, two fermions cannot occupy the same state, whereas bosons tend to occupy the same state. A laser is based on the fact that particles of light — photons — are also bosons. According to quantum mechanics, a composite particle consisting of an even number of fermions behaves as a bosonic matter wave. So we can imagine building a laser or amplifier for such a matter wave. Writing in *Physical Review Letters*, Savvidis *et al.*[1] describe how they amplify matter waves in semiconductors.

The composite particle amplified by Savvidis *et al.* is known as an exciton–polariton. An exciton is a bound state of a negatively charged electron and a positively charged hole, which is analogous to a hydrogen atom. Semiconductors can create them by absorbing photons. Eventually the electron and hole in the exciton will recombine to produce a photon. But if the photons emitted by the excitons in the semiconductor are confined in a reflective microcavity, the excitons and photons are mixed together to create a quasiparticle called a polariton (Fig. 1, overleaf). This new particle is part light and part matter, and consequently the polariton mass is reduced by four orders of magnitude compared with the exciton mass.

Unlike a photon, a massive particle cannot be created from a vacuum. The total number of massive particles must be conserved. In order to amplify a matter wave, a reservoir of identical particles is needed. Moreover, a scattering mechanism to transfer a reservoir particle into the ground state is essential. If the particle is a pure boson without charge, for example a photon in vacuum, there is no such scattering mechanism. But composite bosons, such as excitons, scatter with each other owing to the fermionic nature of their constituents — electrons and holes. This non-bosonic feature of a composite particle is the gain mechanism for a matter-wave amplifier.

In the experiment of Savvidis *et al.*[1],

100 YEARS AGO

The widespread invasion and persistent devastations of locusts in so many parts of Africa give interest to all trials and experiments, as well as the ordinary remedies, employed for the alleviation of this ruinous plague of the farmer. The following notes from Mr. W. C. Robbins, Stock Inspector of the Lower Tugela and Mapumulo Districts, are published in the Cape official *Agricultural Journal*:- "For the past three days I have been over the ground where my men have been infecting locusts with Government fungus, and the result was that I found dead locusts everywhere. I send you a sample; you will notice they are full of worms, and we know from experience that when locusts are found in this state whole swarms die off. Some you will see, are half eaten; these were eaten by their fellows. I have seen many clusters of locusts eating dead ones." The feeding upon bodies of dead locusts suggests that diseased locusts may be utilised as a substitute for locust fungus.

From *Nature* 7 June 1900.

50 YEARS AGO

The gestural or 'ta-ta' theory of the origin of language has a long pedigree, beginning with Plato and achieving its most notable modern exponent in Sir Richard Paget. That Prof. Jóhannesson had been attracted to this theory was evident from his earlier work, "Um Frumtungu Indógermana og Frumheimkynni"; and the dedication of this new volume to Sir Richard sets the author decisively among those who believe themselves capable of demonstrating that language originated in the imitation by the vocal organs of physical shapes and movement. This theory represents one branch of the more general doctrine which sees a natural connexion between things and their names: and it is not to be denied that certain sound-complexes seem, in fact, to be particularly appropriate to the representation of certain shapes — a field of study in which Koehler and the *Gestalt* psychologists have collected some interesting data. But even supposing that these sound-complexes could be shown to involve vocal movements related to the shapes concerned, this would teach us nothing about the origin of language, which must be far remote from the attested or 'reconstructed' forms on which the theory is based — though Prof. Jóhannesson gives one the impression that he believes his hypothetical Indo-European forms at least to approximate to a primitive tongue.

From *Nature* 10 June 1950.

two polaritons with the same quantum wavenumber are simultaneously created by a coherent laser pulse (the 'pump' pulse). These two polaritons are scattered to different energy states — the ground state and a higher-energy state — in a way that conserves energy and momentum between the initial and final states. When the ground-state polariton is stimulated by another coherent laser pulse, an enormous gain of up to 100 is observed.

This might seem like a matter-wave analogue of a laser amplifier. However, it does not correspond to a laser amplifier in an exact sense, but rather to a 'parametric' amplifier. In the radiowave, microwave and optical-wave spectrum, there are always two types of amplifier: a negative-conductance amplifier and a nonlinear-susceptance amplifier. A negative-conductance amplifier is an incoherent system, in which only the energy of the pump pulse determines the system dynamics. A laser amplifier is a classic example of a negative-conductance amplifier. A nonlinear-susceptance amplifier is a coherent system in which both the amplitude and the phase of the pump pulse determine the system dynamics. A parametric amplifier is a classic example of a nonlinear-susceptance amplifier. In the experiment of Savvidis *et al.*[1], the ground-state polariton is amplified by a phase-coherent parametric process.

In a different study, Huang *et al.*[2] create a direct matter-wave analogue of a laser amplifier using essentially the same structure as Savvidis *et al.* In this experiment, two reservoir polaritons with opposite quantum wavenumbers are scattered to the ground and excited states with zero wavenumber. Amplification is observed even after the reservoir polaritons lose the phase information of the pump laser and reach thermal equilibrium. This means that matter-wave amplification in this system could be achieved using electrically injected incoherent excitons.

Matter-wave amplifiers using atoms[3,4] rather than excitons operate on the same principle, but their working conditions are quite different. The effective temperature of an exciton reservoir is about 10 K, whereas that of an atomic reservoir (Bose–Einstein condensate) is about 10 nK. The gain and loss rates of an exciton matter-wave amplifier are approximately $10^{12}\ \mathrm{s}^{-1}$, whereas those of an atomic matter-wave amplifier are approximately $10^{5}\ \mathrm{s}^{-1}$. The ratio of the average spacing between two excitons compared to their radius is about 30, whereas that of the average spacing between two atoms to the atomic radius is about 10^{3}. Exciton matter-wave amplifiers operate at a much higher temperature, gain and particle density than their atomic counterparts.

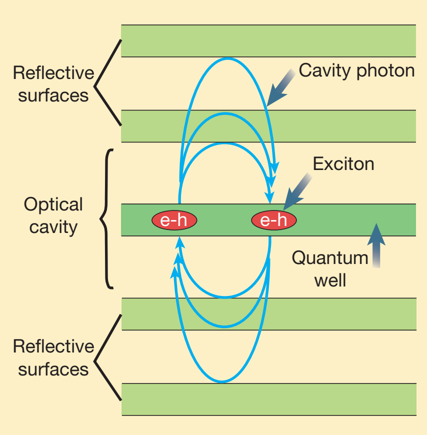

Figure 1 **A semiconductor matter-wave amplifier. Here, a semiconductor quantum well is sandwiched between two reflective microcavities, which are separated by one-half or one wavelength. An exciton, which is a bound state of an electron–hole (e–h) pair and the solid-state analogue of a hydrogen atom, is confined in the quantum well by the potential barrier between the quantum well and the surrounding materials. A light field is trapped by multiple reflection from the reflective interfaces. When a quantum-well exciton and a cavity photon couple strongly with each other, they form a new quasiparticle called a polariton. Savvidis *et al.*[1] show that the polaritons can be excited resonantly by a laser producing amplification of the signal.**

The exciton laser and amplifier can operate with a much smaller pump power than a normal photon laser. A photon laser and amplifier requires more populations in an excited state than in the ground state (so-called population inversion). But the exciton laser and amplifier operate without inversion[5]. A wide bandgap semiconductor, such as gallium nitride or zinc oxide, is more suitable for constructing such an exciton laser and amplifier because the excitons in such materials are stable at higher temperatures and densities. Such semiconductor lasers are attractive because they are an efficient source of blue light.

If the gain of a matter-wave amplifier exceeds the loss rate, the system is expected to form a matter-wave laser (boser)[5]. But the spontaneous build-up of a coherent matter wave without continuous pumping by an input matter wave has yet to be seen. Photoluminescence studies of microcavities in semiconductor quantum wells[6,7] suggest that this goal is within the reach of current technology. ■

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