Despite this promising prospect, the question remains as to whether a reduction in Aβ explains the protective effect of the gene variant identified by Jonsson and colleagues. Here, it is worth keeping in mind a previously identified Alzheimer's-disease-causing mutation, the A673V *APP* gene variant[7]. This mutation increases Aβ generation but causes dementia only in people in which both gene copies are mutated, not just one. It also affects not only the amount, but also, and importantly for this discussion, the biophysical properties of the Aβ that is generated. It seems that the mutated protein interacts with wild-type Aβ to prevent the generation of toxic Aβ assemblies. Given that another mutation at the same site in the APP protein also affects the aggregation properties of Aβ peptides[12], the possibility that Jonsson and colleagues' A673T mutation exerts its protective effects by altering Aβ aggregation should be considered. This more qualitative concept of Aβ toxicity contrasts with the idea that only an increase in Aβ levels can cause disease — and evidence supporting this insight is rapidly mounting[13].

Further work is certainly needed to verify whether the A673T mutation protects against age-related cognitive decline. Jonsson *et al.* report that A673T carriers perform better in cognitive tests than do control subjects, but one wonders whether this can be confirmed by other measurements of cognitive function, and whether confounding factors complicate the interpretation of the reported result. For example, although there were no known cases of Alzheimer's disease in the control population, many other conditions, such as Parkinson's disease or depression (which were not excluded in this assessment), can also negatively affect mental capacity. So Jonsson and colleagues' proposal[6] that "Alzheimer's disease may represent the extreme of the age-related decline in cognitive function" may yet prove to be a premature interpretation of their findings.

Nevertheless, the identification of a protective *APP* gene variant is certainly exciting, and it will be interesting to watch for the identification of other protective gene variants, for example, mutations in the gene encoding β-secretase that might inhibit its expression or its proteolytic activity. As with many genetic findings, more years of hard work will be needed to assess the clinical and therapeutic implications of such findings. But if the preliminary — and quite spectacular — conclusions of Jonsson *et al.* regarding the mechanism of action of the A673T mutation, and its implications for cognition, can be confirmed, then a lifelong suppression of Aβ production by as little as 20% may one day become the 'fountain of youth' for the brain. ■

Bart De Strooper *and* **Thierry Voet** *are in the Center for Human Genetics and Leuven Research Institute for Neurodegenerative Disorders, KU Leuven, 3000 Leuven, Belgium.* **B.D.S.** *is also at the VIB Center for the Biology of Disease, Leuven.*
e-mail: bart.destrooper@cme.vib-kuleuven.be

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B.D.S. declares competing financial interests.
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QUANTUM OPTICS

Strongly interacting photons

A fine marriage between atomic and optical physics has produced a medium that is transparent to single photons but opaque to multiple photons. The finding heralds the development of devices such as single-photon switches. SEE LETTER P.57

THAD G. WALKER

Can photons be made to interact strongly with each other? Until recently, materials with nonlinear optical properties could mediate photon–photon interactions that were weak at best. These weak interactions have previously been artificially enhanced using devices known as optical cavities[1], which make the photons repeat their encounters thousands to millions of times. On page 57 of this issue, Peyronel *et al.*[2] demonstrate a new material in which single photons propagate freely, but interact so strongly with each other that when just two photons are present one is quickly absorbed. The result opens up the possibility of realizing concepts such as single-photon switches, deterministic photon-based quantum logic, and quantum gases of strongly interacting photons*.

We have known since the dawn of quantum physics a century ago that light consists of particles, called photons, of energy hf, where h is Planck's constant and f is the light's frequency. Photons usually interact extremely weakly with each other, but strongly with the charged particles that comprise matter. In most materials, the optical response is linear — a beam comprised of many photons scatters and moves from place to place in the same way that single photons do. Inside nonlinear materials, however, the optical response is altered when multiple photons are present. The motion of a particular photon depends on the properties — most notably the number — of other photons in its vicinity. Until recently, however, available nonlinear materials required large numbers of photons to be present in order for them to noticeably affect each other. Peyronel *et al.*[2] combined several recent developments in atomic and optical physics to produce a novel nonlinear medium that is transparent to single photons yet opaque to multiple photons (Fig. 1).

The largest nonlinear optical effects achievable in atoms occur when a light field renders the atoms transparent. Consider a sample of atoms that have three energy levels: a ground state E_g, an excited state E_r and an intermediate level E_e (see Fig. 1b of the paper[2]). Photons of frequency f_1 that are directed into the sample and obey the Bohr equation, $hf_1 = E_e - E_g$, will normally be absorbed. However, when a strong 'control' laser of frequency f_2 is also shone on the sample, the atoms become transparent to frequency f_1 if the condition $h(f_1 + f_2) = E_r - E_g$ is satisfied. This electromagnetically induced transparency (EIT; ref. 3) puts the atoms and photons into collective excitations called polaritons. In Peyronel and colleagues' experiment, the control laser changes the transmission of the atomic gas from essentially zero to 60%. The EIT condition is extremely sensitive: photons that obey it are transmitted with high probability, whereas those that violate it are absorbed normally. This is basically an optically controlled switch[4].

When the upper level r is a state of large

*This article and the paper under discussion[2] were published online on 25 July 2012.

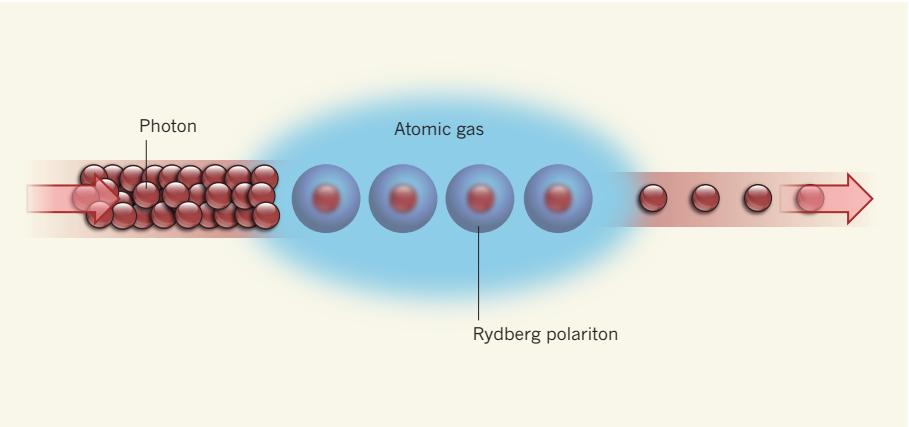

Figure 1 | A stream of single photons. Peyronel *et al.*[2] have directed a beam of overlapping photons into an atomic gas in which single photons are converted into collective excitations known as Rydberg polaritons. The polaritons, which can be thought of as spheres comprising many atoms and one photon, strongly absorb additional photons. On exiting the gas, the polaritons are converted back to individual, non-overlapping photons.

principal quantum number n (a Rydberg state[5]), the EIT condition can be easily violated by weak interactions between the atoms. For an n of about 100, a single Rydberg atom will cause a violation of the EIT condition for all other atoms within a 'blockade radius' of 10 micrometres. This Rydberg blockade produces record nonlinearities, as shown recently by Adams and colleagues[6], and has been used to entangle neutral atoms separated by micrometre-scale distances[7,8]. A Rydberg polariton can be thought of as a 10-μm sphere containing many ground-state atoms and one Rydberg atom — or, equivalently, many atoms and one photon. Should other photons enter a volume already occupied by a Rydberg polariton, the blockade effect causes a violation of the EIT condition, so the photons are absorbed rather than transmitted. Note that if the atom density is low, as in previous experiments[6], the absorption probability may still be small.

The final, essential ingredient needed to generate strong photon–photon interactions at the two-photon level is an atomic cloud of such high density that when two or more photons enter a blockade volume, all but one are absorbed within that volume, leaving a single Rydberg polariton. This 'photon blockade' is the novelty of Peyronel and colleagues' study. Their experiment reveals that a multi-photon incident light beam is converted, within a few micrometres, into a beam of single photons, with a small (less than 0.09) probability that two photons will leave the atomic gas at the same time. Interestingly, even though their sample is large enough for several Rydberg polaritons to coexist, the authors find that (and explain why) only one photon at a time is found within the entire sample.

An exciting feature of this experiment is that there are several clear avenues towards improving the properties of the medium. Cooler, denser atomic gases and lasers that have a narrower frequency range would improve the EIT transmission to nearly 100% and reduce the overlap of photons from the single-photon source. A looming challenge is to reconfigure the experiment so that the two-photon nonlinearity delays rather than absorbs excess photons[6]. This type of nonlinearity, which preserves the number of photons, would be extremely useful for quantum-information purposes.

In one respect, Peyronel and colleagues have demonstrated a quality single-photon light source that has a rate of emission in the megahertz regime, as Dudin and Kuzmich have shown[9] using a related approach. The key capability of this experiment[2] — engineering strong photon–photon interactions at the two-photon level — should also lead to various other new possibilities. For example, single-photon switches, photon detectors of high quantum efficiency, and non-destructive photon detection can easily be foreseen as extensions of this work. The physics of strongly interacting photons has a bright future. ■

Thad G. Walker *is in the Department of Physics, University of Wisconsin-Madison, Madison, Wisconsin 53706, USA.*
e-mail: tgwalker@wisc.edu

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SYSTEMS BIOLOGY

A cell in a computer

The small genomes of some bacteria could provide the first complete understanding of a biological system. A new computer model brings this goal closer, by calculating every process in a dividing *Mycoplasma* cell.

MARK ISALAN

It has long been a dream in biology to push reductionism to the limit: to describe a cell as a set of interacting components and to capture whole-cell behaviour in a computer model. A good model doesn't simply recapitulate the observed behaviours that are fed into it. Rather, the aim is to predict the unknown effect of any novel perturbation or mutation. Such goals are very ambitious because of the challenge of attempting to obtain quantitative information on every one of the cell's gene products and metabolites. Nevertheless, Karr *et al.*[1], writing in *Cell*, present the most comprehensive model of a bacterial cell cycle so far, built on the basis of individual molecules and their relationships. Impressively, the model can predict gene-expression levels and cell-replication times in the challenging context of mutations involving gene deletions.

Mycoplasma genitalium is a urogenital bacterial parasite that has only 525 genes, making it one of the smallest genomes of any independently dividing cell — for comparison, the gut bacterium *Escherichia coli* has around 4,000 genes. Because of their status as one of the 'simplest' cells, *Mycoplasma* species are rapidly becoming the most measured biological systems in history, and full descriptions of their molecular content, in terms of DNA, RNA, protein and metabolites, are available[2–4]. The cells are therefore considered to be the ideal target for whole-cell modelling[5].

What is striking about Karr and colleagues' model is the sheer ambition of its scale and its attention to detail. The authors retrieved (and in some cases retested) more than 1,900 experimentally derived cellular parameters, such as enzymatic reaction rates and protein-binding