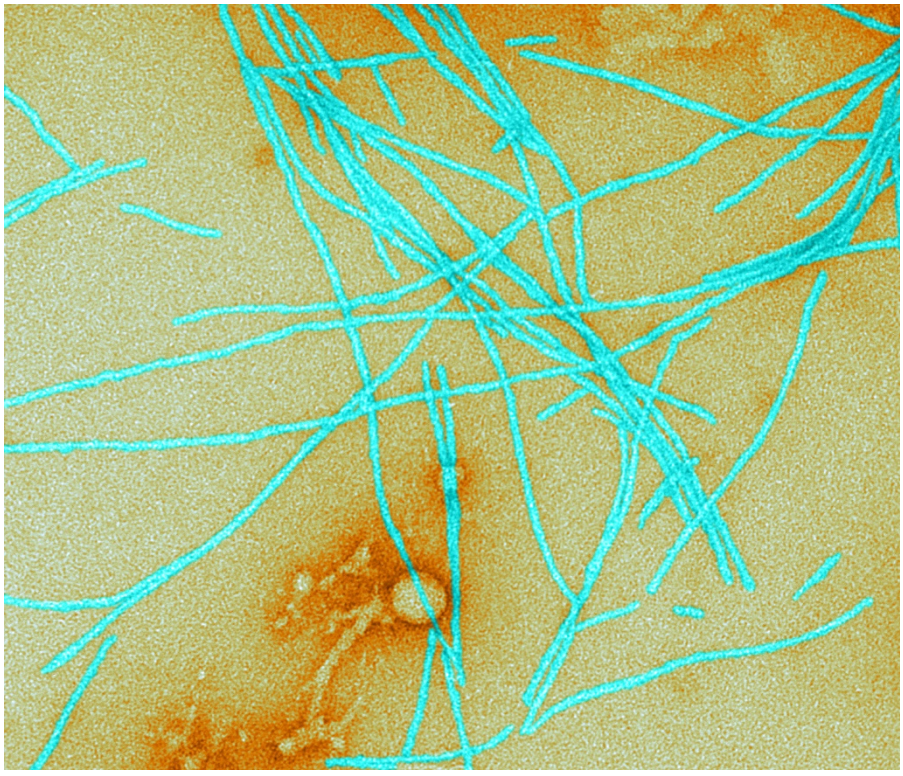

Science Source

Fluorescent fibrils: Long, thin amyloid fibrils make up amyloid deposits.

to help clear amyloid from the body. The small-molecule drug that Pepys developed to clear SAP from amyloid, now-called miridesap, was patented in 1998. "Miriam is my daughter's name, and this drug works to deplete SAP," Pepys says. Normal SAP, which exists as a single molecule, isn't recognized by the liver, but miridesap is designed in such a way that two SAP molecules bind to either end of the drug. The liver recognizes this configuration as abnormal, according to Pepys, and proceeds to digest the SAP–miridesap complex. SAP is thus cleared from the body.

> "There's so much we don't know about these diseases that it's really dangerous to definitively say that only one thing is going on."

Although blood tests and imaging indicated that miridesap removed large amounts of SAP from the amyloid deposits, a follow-up study by Pepys' team found that there was still lingering SAP in the amyloid deposits in patients and the amount of amyloid in these patients was unchanged (*Br. J. Haematol.* **148**, 760–767, 2010). As such, Pepys and his team set out to develop an antibody to be used in combination with miridesap that would cling to SAP and flag the amyloid so that the body's phagocytes could be alerted to the presence of amyloid and clear these deposits. Pepys licensed both miridesap and the anti-SAP antibody to GSK in 2009, and the combination was tested in 15 patients, including the famed Patient 8, in 2013. The results of the phase 1 study, published in 2015, revealed that treatment with miridesap, followed by treatment with the anti-SAP antibody, significantly cleared amyloid and improved liver function (*N. Engl. J. Med.* **373**, 1106–1114, 2015). As *Nature Medicine* went to press, a phase 2 trial of the combination was about to begin, with a projected study completion date of May 2020.

Even as treatments aiming to curtail the accumulation of amyloid fibrils in the body move forward, some experts wonder whether solely targeting these protein clumps is enough. In amyloidosis, they question whether the precursor misfolded proteins drive damage to cells, or whether it only happens when the proteins combine together to form fibrils. Several patients who have taken tafamidis for years have seen clinical benefit without any evidence that the drug has cleared existing amyloid buildup in their bodies, Kelly notes. He thinks that, even if amyloid fibrils are causing disease, something else is also contributing to the pathology.

Even those who see the aberrant protein clumps as the main culprit concede that methods for ridding the body of these deposits might still be years away from receiving regulatory approval. Researchers are still teasing apart the normal function of the 30-odd proteins that cause the more than 30 types of amyloidosis. "We rarely know all the functions of any given protein," Kelly says, "and each protein does multiple things." Although there is redundancy built into protein functions, Kelly adds, the approach of eliminating amyloid-protein production altogether may prove to be shortsighted.

Those in the Alzheimer's disease field are also watching the amyloidosis research. David Knopman, chair of the medical and scientific advisory council of the nonprofit Alzheimer's Association, says that his group will be curious to see whether the treatments for amyloidosis prove successful at curbing protein production and removing amyloid. But, he adds, it's very early on, and there might not be any takeaways for the treatment of Alzheimer's disease.

Many in the amyloidosis community are hopeful that the efforts currently under way will be fruitful, but some are still reserved in their optimism. "Amyloidosis is a lot more complicated than we can ever imagine," Solomon says. And despite advancements in technology that have enabled a new wave of drugs and improved our understanding of amyloidosis, he says, "we have a long way to go."

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Correction

In the January 2017 issue, the piece "Living therapeutics: Scientists genetically modify bacteria to deliver drugs" (*Nat. Med.* **23**, 5–7, 2017) incorrectly stated that the company Oragenics is slated to launch a phase 2 trial on ulcerative mucositis next year. In fact, they will begin the trial in 2017. The error has been corrected in the HTML and PDF versions of this article.