



NEWS



RESEARCH HIGHLIGHTS



INTERVIEW



## Unconventional trafficking pathway may lead to cystic fibrosis therapeutics

Researchers have provided insight into how an alternative, 'unconventional' pathway can correct aberrant protein trafficking in cystic fibrosis. The study, published in *Cell*, may offer a potential therapeutic strategy for the treatment of cystic fibrosis.

The most prevalent disease-causing mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) protein is the deletion of Phe508 ( $\Delta F508$ ), with resultant defects in conventional Golgi-mediated exocytosis and cell surface expression of the mutated protein. The team found a novel method to rescue this defect in mice, which directs the  $\Delta F508$ -CFTR protein to the cell surface *in vitro* and *in vivo* using an unconventional GRASP-dependent secretion pathway associated with endoplasmic reticulum stress. Transgenic expression of GRASP in  $\Delta F508$ -CFTR mice restored ion transport levels to more than 60% of those seen in normal, healthy mice and rescued mouse survival without any clear toxicity.

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Cystic fibrosis is caused by mutations in the gene *CFTR*, which encodes a protein channel, CFTR, usually located on the surfaces of cells lining the airway and intestine. This protein is responsible for the transport of ions across cell membranes but in patients with the disease, the channels are not effectively transported to the

cell surface. As a result ions and fluids cannot pass in and out of cells as they should, causing mucus build-up and chronic lung infections.

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This study identifies an alternative way to send the mutant proteins to the surface, thus restoring ion transport. A protein normally localized to intracellular membranes, GRASP65, is sequestered to escort mutant CFTR channels to the cell surface by following an alternative route. "Many have searched for the so-called CFTR correctors that can aid the surface expression of mutant CFTR through conventional trafficking," explained Min Goo Lee (Yasei University College of Medicine, Seoul Republic of Korea), senior author of this study. "Some molecules have shown promise in the laboratory, but none have led to the development of commercially available therapies so far." This study is the first to demonstrate the potential of an alternative trafficking pathway as a therapeutic for cystic fibrosis. Lee was positive about the findings: "We hope this could turn out to be a giant leap in future clinical medicine, especially for treating human genetic diseases."

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 Sources: [www.eurekalert.org/pub\\_releases/2011-09/cp-ap082911.php](http://www.eurekalert.org/pub_releases/2011-09/cp-ap082911.php); Gee HY, Noh SH, Tang BL, Kim KH, Lee MG. Rescue of  $\Delta F508$ -CFTR trafficking via a GRASP-dependent unconventional secretion pathway. *Cell* 146(5), 746-760 (2011).



## Women and the poor with cystic fibrosis still have worse prognosis, according to recent report

Survival from cystic fibrosis in England and Wales is still strongly determined by socioeconomic status and sex; an association that has not substantially changed over the years.

A recent report published in the *British Medical Journal* details a cross-sectional study aimed to determine the trend in the association between socioeconomic status and sex and median age at death from cystic fibrosis in England and Wales, over the past 50 years. The authors from the University of Nottingham (Nottingham, UK) analyzed mortality data for cystic fibrosis from the Office for National Statistics collected between 1959 and 2008.

In this time a total of 6750 recorded deaths were attributed to cystic fibrosis in England and Wales. However, contrary to the authors' hypothesis that improvements in healthcare provision would lessen the effect of socioeconomic status and sex on median age at death from cystic fibrosis, these effects remained: males were more likely to die above the annual median age at death than females, and individuals in the highest socioeconomic class were also more likely to die above the median

age of death than those in the lowest socioeconomic class.

The premise of the study stems from the identification of disparities in outcome between high and low socioeconomic status in individuals with a diagnosis of cystic fibrosis over 20 years ago. Over the past 50 years, survival in individuals with cystic fibrosis has improved significantly, with the median age at death rising from 6 months in 1959 to 27 years in 2008. This has been attributed to considerable improvements in multidisciplinary healthcare provision including improved early diagnosis, nutrition, infection control and antibiotic treatments. Yet high socioeconomic status has been presented as a marker of good prognosis in cystic fibrosis. Moreover, an association between female sex and impaired prognosis in cystic fibrosis has also been well described; numerous studies in the UK and the USA have demonstrated significant differences in survival between sexes.

The findings of this study indicate that these effects persist in the 21st century and are still strong, despite the healthcare advances and overall improvements in mortality. However, the reasons for the

persistence remain unclear, but the authors suggest that the intersex disparity in survival may be due to a greater propensity for women to develop infection or other complications of cystic fibrosis. On the other hand, socioeconomic status is more difficult to explain because it is composed of multiple measures but the authors offer factors, such as lifestyle, education and access to healthcare as possible reasons for this trend.

In any case, the authors conclude that healthcare workers must be aware of these disparities to enable early intervention and screening. In addition, author Helen Barr (University of Nottingham, Nottingham, UK) suggests that "research into the etiology of the socioeconomic health gap is warranted to identify factors which may be amenable to intervention such as environmental tobacco smoke and access to healthcare".

Source: Barr HL, Britton J, Smyth AR, Fogarty AW. Association between socioeconomic status, sex, and age at death from cystic fibrosis in England and Wales (1959 to 2008): cross sectional study. *BMJ* doi: 10.1136/bmj.d4662 (2011) (Epub ahead of print).

## Cystic fibrosis treatment under threat from £6 million cash deficit

A desperate push to save a £36 million UK project aiming to develop an effective gene therapy for cystic fibrosis is set to be launched. The necessary sum required is estimated by researchers and campaigners at £6 million in the next 6 weeks.

The UK Cystic Fibrosis Gene Therapy Consortium was founded in 2001 and it was, explained the consortium's co-ordinator Professor Eric Alton (London, UK), "Because the CF trust, who have until

recently been providing the bulk of our funding, were funding three UK groups at Imperial College London, the University of Oxford and the University of Edinburgh, who were in competition. Rosie Barns, the former Chief Executive of the CF Trust, had the very good idea of bringing us all together one evening and suggesting that it would be much more efficient if we worked together." The consortium is focused on developing vectors to deliver the wild-type

*CFTR* gene to cystic fibrosis patients and restore normal respiratory function. The collaboration functions "more like a small pharmaceutical company than a group of academics" says Alton, because they have a product pipeline and are continually looking for alternative therapeutic pathways to investigate.

The consortium is currently developing two primary product "waves", delineated in to wave 1, a liposome gene vector



going into a clinical trial next year, and wave 2, a lentiviral vector that is expected to “be online in around 4 years time or so,” according to Alton. Within each of these waves are a number of subprojects involved in activities, such as patient recruitment and identifying the best nebulizer and biomarkers.

Unfortunately, the current economic downturn has crippled the funding body the CF trust, and as the researchers began to initiate a second phase of clinical trials to compare the effects of the gene therapy treatment with a placebo they lost virtually all their funding. “This has really slowed things over the past year because we have spend the whole year not doing science and or seeing patients, and just scrabbling around trying to find money,” explained Alton. “There is no question that

it has slowed us down by a year at least. Currently we do not have any funding certainty to do the trial. Unless we raise the last £6 million by the end of October, we will have to lay off staff,” he added.

Should the project, which has involved more than 80 scientists, fail, it will be abandoned because as Alton explains, “The medicines we have developed to treat patients have a limited storage life and will have to be thrown away. We will have to disband – with our target in sight”, thus dashing the hopes of the many young sufferers of this incurable wasting disease. Consequentially, the trust is launching a ‘CF Sprint’ campaign to raise money from the public. Concurrently, the researchers have applied to pharmaceutical companies and government grant bodies for aid. “I cannot believe that all this work we have

done, after the ‘herculean’ efforts that have been made, will be allowed to collapse,” said Matthew Reed, Chief Executive of the Cystic Fibrosis Trust. “In the scheme of things, £6 million is not a vast sum though it is a very tough goal for a charity to raise in such a short space of time. We have to succeed.”

Sources: [www.guardian.co.uk/science/2011/sep/18/cystic-fibrosis-cure-cash-threat](http://www.guardian.co.uk/science/2011/sep/18/cystic-fibrosis-cure-cash-threat); Alton E. *Gene therapy for cystic fibrosis: future hopes and milestones*. *Therapy* 8,(6), 607–611 (2011).

## Deletion of the ubiquitin ligase Nedd4L in lung epithelia causes cystic fibrosis-like disease

A team of researchers at The Hospital for Sick Children (SickKids) in Toronto, Ontario, Canada, has identified a role of the ubiquitin ligase Nedd4L in cystic fibrosis; a promising step towards understanding the molecular pathophysiology of the disease.

Daniela Rotin and colleagues demonstrated in mice that knockout of Nedd4L (Nedd4–2) specifically in lung epithelia (surfactant protein C-expressing type II and Clara cells) causes cystic fibrosis-like lung disease, with airway mucus obstruction, goblet cell hyperplasia, massive inflammation, fibrosis and death by 3 weeks of age. In addition, the increased epithelial Na<sup>+</sup> channel (ENaC) protein levels, lung dryness at birth, amiloride-sensitive dehydration of lung explants, and elevated ENaC currents in primary

alveolar type II cells detected by the authors led them to conclude that the deleterious effects of Nedd4L loss are likely caused by enhanced ENaC function. The authors were able to rescue these lung defects by administration of amiloride into the lungs of young knockout pups via nasal instillation, underscoring the therapeutic potential of this pathway.

Impaired ion transport due to mutated cystic fibrosis transmembrane conductance regulator is accompanied by elevated activity of the amiloride-sensitive epithelial ENaC. This causes the lung epithelial cells to absorb excessive Na<sup>+</sup> via a protein known as ENaC, leading to more viscous mucus that blocks oxygen exchange and causes difficulty breathing; the lungs are unable to flush the mucous (and trapped bacteria) out and this leads to increased

respiratory tract diseases. Previous research has indicated that Nedd4L suppresses ENaC activity.

These results provide evidence for this mechanistic link, suggesting that Nedd4L can suppress the onset of cystic fibrosis symptoms by inhibiting ENaC in lung epithelia. According to Rotin, the results may present therapeutic opportunities for developing treatments for cystic fibrosis: “If you can enhance Nedd4L function or increase the amount of Nedd4L in the lungs, which may be useful in alleviating symptoms of the disease. Another option is to inhibit ENaC.”

Sources: Kimura T, Kawabe H, Jiang C et al. *Deletion of the ubiquitin ligase Nedd4L in lung epithelia causes cystic fibrosis-like disease*. *Proc. Natl Acad. Sci. USA* 108(8), 3216–3221 (2011); [www.eurekalert.org/pub\\_releases/2011-09/aps-uan091911.php](http://www.eurekalert.org/pub_releases/2011-09/aps-uan091911.php)

### About the News and Views

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