

Small-molecule modulators of CFTR function discovered by high-throughput screening

Alan S. Verkman, Nitin D. Sonawane, Gergely L. Lukacs, Chatchai Muanprasat, Nicoletta Pedemonte, Luis J.V. Galiotta

Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA, 94143-0521, USA, Program in Cell Biology, Hospital for Sick Children Research Institute and University of Toronto, Ontario, Canada M5G 1X8, and Laboratorio di Genetica Molecolare, Istituto Giannina Gaslini, 16148 Genova, Italy

(available free on line at: www.actabiomedica.it)

The Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) is a cAMP-activated chloride channel expressed in epithelia in the lung, intestine, pancreas, testis and other tissues, where it facilitates transepithelial fluid transport. In the intestine CFTR provides the major route for chloride secretion in certain diarrheas. Mutations in CFTR cause the hereditary disease cystic fibrosis, where chronic lung infection and deterioration in lung function cause early death. CFTR is a well-validated targeted for development of inhibitors for therapy of secretory diarrheas and activators for therapy in cystic fibrosis. Our lab has identified and optimized small molecule inhibitors of CFTR, as well as activators of $\Delta F508$ -CFTR, the most common mutant CFTR causing cystic fibrosis. High-throughput screening of small molecule collections utilizing a cell-based fluorescence assay of halide transport yielded thiazolidinone and glycine hydrazide CFTR inhibitors that block enterotoxin-mediated secretory diarrhea in rodent models, including a class of non-absorbable inhibitors that target the CFTR pore at its external entrance. Benzothiophene, phenylglycine and sulfonamide potentiators were identified that correct the defective gating of $\Delta F508$ -CFTR chloride channels, and other small molecules that correct its defective cellular processing. Small molecule modulators of CFTR function may be useful in the treatment of cystic fibrosis, secretory diarrhea and polycystic kidney disease.

References

1. Ma, T., J.R. Thiagarajah, H. Yang, N.D. Sonawane, C. Folli, L.J. Galiotta and A.S. Verkman (2002). Thiazolidinone CFTR inhibitor identified by high-throughput screening blocks cholera-toxin induced intestinal fluid secretion. *J. Clin. Invest.* 110: 1651-1658.
2. Yang, H., A.A. Shelat, R.K. Guy, V.S. Gopinath, T. Ma, K. Du, G.L. Lukacs, A. Taddei, C. Folli, N. Pedemonte, L.V. Galiotta and A.S. Verkman (2003). Nanomolar affinity small-molecule correctors of defective $\Delta F508$ -CFTR chloride channel gating. *J. Biol. Chem.* 278: 35079-35085.
3. Thiagarajah, J., T. Broadbent, E. Hsieh and A.S. Verkman (2004). Prevention of toxin-induced intestinal ion and fluid secretion by a small-molecule CFTR inhibitor. *Gastroenterology* 126: 511-519.
4. Muanprasat, C., N.D. Sonawane, D. Salinas, A. Taddei, L.J.V. Galiotta and A.S. Verkman (2004). Discovery of glycine hydrazide pore-occluding CFTR inhibitors: mechanism, structure-activity analysis and in vivo efficacy. *J. Gen. Physiol.* 124: 125-137.
5. Pedemonte, N., G.L. Lukacs, K. Du, E. Caci, O. Zegarra-Moran, L.J. Galiotta and A.S. Verkman (2005). Small molecule correctors of defective $\Delta F508$ -CFTR cellular processing identified by high-throughput screening. *J. Clin. Invest.* 115: 2564-2571.
6. Sonawane, N.D., J. Hu, C. Muanprasat and A.S. Verkman (2006). Luminally-active non-absorbable CFTR inhibitors as potential therapy to reduce intestinal fluid loss in cholera. *FASEB J.* 20: 130-132.

Correspondence: Alan S. Verkman
Departments of Medicine and Physiology,
University of California, San Francisco, Ca, USA
E-mail: verkman@itsa.ucsf.edu