Am J Physiol Lung Cell Mol Physiol 307: L431–L434, 2014;
First published July 25, 2013; doi:10.1152/ajplung.00177.2014.

Rescuing ΔF508 CFTR with trimethylangelicin, a dual-acting corrector and potentiator

James F. Collawn,[1,3,4] Lianwu Fu,[1,4] Rafal Bartoszewski,[5] and Sadis Matalon[1,2,3,4]

[1]*Department of Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, Alabama;* [2]*Department of Anesthesiology, University of Alabama at Birmingham, Birmingham, Alabama;* [3]*Pulmonary Injury and Repair Center, University of Alabama at Birmingham, Birmingham, Alabama;* [4]*Cystic Fibrosis Research Center, University of Alabama at Birmingham, Birmingham, Alabama; and* [5]*Department of Biology and Pharmaceutical Botany, Medical University of Gdansk, Gdansk, Poland*

Submitted 2 July 2014; accepted in final form 4 July 2014

Collawn JF, Fu L, Bartoszewski R, Matalon S. Rescuing ΔF508 CFTR with trimethylangelicin, a dual-acting corrector and potentiator. *Am J Physiol Lung Cell Mol Physiol* 307: L431–L434, 2014. First published July 25, 2013; doi:10.1152/ajplung.00177.2014.—Since the discovery of the cystic fibrosis (CF) gene that encodes the CF transmembrane conductance regulator (CFTR) in 1989, there has been considerable progress in understanding the molecular defects associated with different mutations in the CFTR protein. Small molecule "potentiators" have led the way as a drug therapeutic approach for correcting channel gating mutations such as the G551D mutation. Therapies for correcting the most common folding mutation in CFTR, ΔF508, however, have proven to be much more challenging. The protein-folding problem appears to be associated with both nucleotide binding domain (NBD) instability and domain interface interactions that are caused by the loss of the phenylalanine residue in NBD 1. Given the inherent complexity in the sequential folding pathway for this very large multidomain protein, it has been suggested that correcting the proper folding, anion channel function, and cell surface stability of the ΔF508 CFTR protein will require a multidrug approach to fix each of these compounding problems. Here we discuss a recent publication (Favia M, Mancini MT, Bezzerri V, Guerra L, Laselva O, Abbattiscianni AC, Debellis L, Reshkin SJ, Gambari R, Cabrini G, Casavola V. *Am J Physiol Lung Cell Mol Physiol* 307: L48–L61, 2014), however, that offers hope that single drug therapies are still possible.

cystic fibrosis; pharmaceutical chaperones; cystic fibrosis transmembrane conductance regulator; IL-8

CYSTIC FIBROSIS (CF) is an autosomal recessive disorder caused by mutations in the CF gene (31). The gene product encodes a protein called the cystic fibrosis transmembrane conductance regulator (CFTR), a 1,480-amino acid protein that is a member of the ATP-binding cassette (ABC) transporter superfamily (30). CFTR is a cAMP-activated anion channel and is composed of two nucleotide-binding domains (NBD1 and NBD2), two membrane-spanning domains (MSD1 and MSD2), a regulator region (R), and four cytosolic loops (CL1–4) (29). More than 1,900 mutations have been identified in the CFTR gene (http://www.genet.sickkids.on.ca/cftr/StatisticsPage.html). ΔF508 CFTR is the most common mutation and this mutation results in the production of a misfolded protein that is degraded by the ubiquitin-proteasome system during biogenesis (2, 39).

Address for reprint requests and other correspondence: J. F. Collawn, Dept. of Cell, Developmental and Integrative Biology, School of Medicine, Univ. of Alabama at Birmingham, 1918 University Blvd., MCLM 395, Birmingham, AL 35294 (e-mail: jcollawn@uab.edu).

Understanding how loss of phenylalanine at position 508 in NBD1 affects the folding of CFTR has turned out to be a complex problem. Although ΔF508 CFTR is subject to ubiquitin-dependent endoplasmic reticulum (ER)-associated degradation during biogenesis, low-temperature incubation (27°C) of cultured cells for 24–48 h facilitates delivery of some maturely glycosylated ΔF508 CFTR to the cell surface (7). And although this maturely glycosylated protein manages to escape degradation, there still appear to be some defects associated with its channel activity and plasma membrane surface stability (3, 5, 12, 13, 18, 33, 38). Despite these additional concerns, there has been considerable effort in the CF field to identify small molecule "correctors" that promote the correct folding and exit of ΔF508 CFTR from the ER and delivery to the plasma membrane (24, 37, 40).

Because of multidomain structure of CFTR, it has been proposed that the sequential folding of CFTR requires the stabilization of both NBD1 energetics and NBD1 interactions between MSD1 and MSD2 (10, 11, 20, 23, 27, 28, 35). This has led to the concept that the different correctors that have been identified can only fix one of the folding defects of ΔF508 CFTR but not others, and therefore these correctors fall into distinct classes or complementation groups (20, 23). This further supports the idea that a combination of drugs is required to fix ΔF508 CFTR. The most promising corrector to date, Vertex 809, increases the functional activity of ΔF508 CFTR in vitro to ~15% of wild-type CFTR in primary human bronchial epithelial cells, and the addition of a "potentiator" such as Vertex 770 that increases channel gating properties of ΔF508 CFTR has additive functional effects (36). Despite these exciting advances, it is unclear whether additional therapeutic approaches will be necessary to achieve the needed therapeutic benefit for patients.

Most approaches have considered combinations of a corrector and a potentiator as described above for the Vertex compounds or, alternatively, combinations of different classes of correctors. The latter strategy has certainly been shown to have additive effects (16). An alternative approach has been to identify single compounds with both corrector and potentiator effects, which has proven to be more difficult, although examples of these have been found (14, 25, 26). One clever approach was to construct a hybrid potentiator-corrector molecule using two known compounds with these activities that would subsequently be cleaved in the intestine into its two bioactive components (21). Another approach has been to identify correctors that also test positive for potentiator activity; CoPo-22 is an example of such a compound (26, 32).

Clearly to date, no one compound is available that appears to be sufficient for demonstrating a clinical benefit in patients expressing ΔF508 CFTR, and therefore the search for drug combinations that push through this apparent therapeutic glass ceiling continues.

A recent paper by Favia et al. (9) continues with this idea of dual-acting compounds, but in this case that is not what the authors were originally searching to find. The initial studies were directed toward identifying compounds that inhibited IL-8 production and the subsequent recruitment of neutrophils into the bronchi of CF patients (22). Given that neutrophils promote lung inflammation and activate sodium channels (1), blocking this response is a key therapeutic target in CF (15). In the initial studies using plant extracts, and then later using purified components from active extracts, the authors identified 5-methoxypsoralen as a compound that inhibited IL-8 expression at a 10 μM concentration in bronchial epithelial cells when these cells were challenged with *Pseudomonas aeruginosa* (22). In their follow-up studies examining analogs of 5-methoxypsoralen, Tamanini et al. (34) found that the most potent analog, 4,6,4′-trimethylangelicin (TMA), inhibited *P. aeruginosa*-dependent IL-8 in the nanomolar concentration range in a number of different human airway epithelial cell lines. Furthermore, because psoralens were known to potentiate CFTR-mediated channel function (8), the authors tested TMA and found that it had potentiator activity (34).

In their most recent study, Favia et al. (9) tested whether TMA can act as a corrector as well, and, if so, how it compares to Vertex 809. Using Fischer rat thyroid (FRT) cells and a fluorescent YFP halide sensor, the authors demonstrated that 48-h treatment with TMA enhanced iodide influx as monitored by fluorescence quenching and found that the maximum activity occurred at a 200 nM concentration. The specific CFTR inhibitor, CFTRinh-172 (19), was used to validate the specificity of this response. Interestingly, the magnitude of the response was greater in the FRT cells with the TMA (200 nM) than with Vertex 809 (10 μM) in these assays. The TMA effect was also shown in polarized CFBE41o-ΔF cells, and, after 24 h of treatment with TMA, the CFTR-dependent chloride efflux was stable for an additional 24 h after drug washout, indicating that the TMA effectiveness appears to be long lasting (9). This suggested that TMA had two important properties of a corrector: it corrected the biogenesis defect and it stabilized ΔF508 CFTR at the cell surface even after drug washout (Fig. 1).

Another important aspect of the corrector treatment is finding compounds that are additive with Vertex 809. The combination therapy with 100 nM TMA and 5 μM Vertex 809 indicated that there was no additive effect, suggesting that both are in the same class of drugs and were acting via a similar mechanism (9). Furthermore, in an effort to directly compare the potentiator activity of TMA to Vertex 770 in polarized CFBE41o-ΔF cells, Favia and colleagues tested acute addition

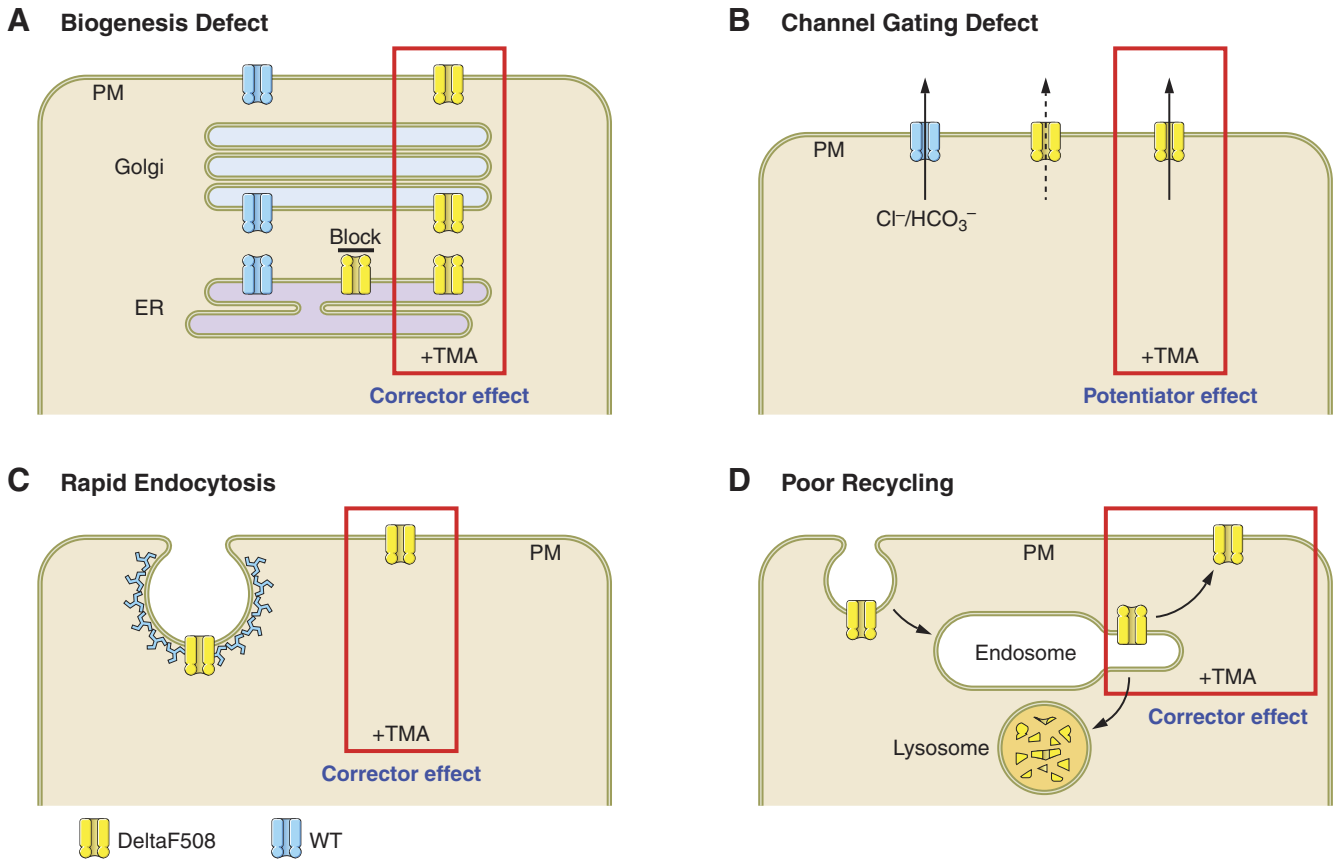

Fig. 1. Trimethylangelicin (TMA) effects on ΔF508 CFTR biogenesis, channel function, and plasma membrane stability. *A*: ΔF508 CFTR biogenesis defect. TMA promotes ΔF508 CFTR folding and exit from the endoplasmic reticulum (ER) and delivery to the plasma membrane (PM) (corrector effect). *B*: ΔF508 CFTR channel gating defect. TMA activates the channel at the plasma membrane (potentiator effect). *C*: ΔF508 CFTR is rapidly endocytosed. TMA inhibits rapid endocytosis (corrector effect). *D*: surface ΔF508 CFTR fails to recycle efficiently and is rapidly degraded at 37°C. TMA presumably promotes efficient recycling (corrector effect) given that the corrected protein is stable at the cell surface for more than 8 h at 37°C. WT, wild-type CFTR.

of 10 μM Vertex 770 vs. 250 nM TMA after a 24-h treatment with 100 nM TMA (9). The results demonstrated that the two acute treatments were comparable (9), further suggesting that TMA effectiveness as both a corrector and potentiator (Fig. 1) were very impressive.

To understand how TMA was working, Favia and colleagues (9) found that TMA treatment had no effect on CFTR mRNA message levels in CFBE41o-ΔF cells but did enhance the levels of both immaturely and maturely glycosylated ΔF508 CFTR protein in a manner similar to Vertex 809. Low-temperature-corrected CFBE41o-ΔF cells that were pretreated with TMA during the last 3 h of low temperature also demonstrated that the TMA effect stabilized the surface pool compared with the vehicle control (Fig. 1), suggesting that TMA treatment was effective even after biogenesis. But the in vitro acid test for a CFTR corrector has always been in testing its effectiveness in polarized monolayers of primary human bronchial epithelial cells derived from ΔF508 CFTR homozygous patients. In these experiments, the wild-type control bronchial epithelial cells were from four healthy donors, and the experimental cells were bronchial epithelial cells derived from four CF donors treated for 24 h with vehicle control or 100 nM TMA (9). The chloride efflux measurements indicated that the CFTR-dependent secretion was almost 40% of the wild-type activity, suggesting that TMA was very effective in primary cells (9). Using an alternative functional test, Favia and colleagues found that Ussing chamber analyses of primary cells supported the fluorescence assay results (9).

Finding a corrector and potentiator within one molecule certainly is an appealing concept. But whether this compound or an analog is sufficient to break through the therapeutic glass ceiling remains to be established. Understanding TMA's mechanism of action is certainly the next step. Furthermore, determining how well this compound works in the primary CF intestinal organoids (6) and in animal models is important as well. Is it possible that a single drug can be used to reverse the lung pathology found in CF patients? Is a single drug a better strategy for patient care than two or more drugs? Could other therapies such as regulation of sodium channels (4, 17) or alternative chloride channels (6) create the needed additional benefit for fixing the lung pathology? Although many questions remain, it is always a good plan to have more than one option.

GRANTS

This publication was made possible by U.S. National Institutes of Health Grants 5R01DK060065 (J. F. Collawn) and 5R01HL031197 (S. Matalon) and by the Ministry of Science and Higher Education of the Republic of Poland, KNOW Program (R. Bartoszewski). L. Fu was supported in part by the North American Cystic Fibrosis Foundation Grant CFF R474-CR11 (Eric Sorscher).

DISCLOSURES

J. F. Collawn has intellectual property rights in an international patent application together with DiscoveryBioMed, Inc. on chemical compounds to be used as potential therapeutics in cystic fibrosis. These compounds, however, are unrelated to the chemical compounds discussed here. No other conflicts of interest, financial or otherwise, are declared by L. Fu, R. Bartoszewski, and S. Matalon.

AUTHOR CONTRIBUTIONS

J.F.C. and S.M. drafted manuscript; J.F.C., L.F., R.B., and S.M. edited and revised manuscript; J.F.C., L.F., R.B., and S.M. approved the final version of manuscript.

REFERENCES

1. **Caldwell RA, Boucher RC, Stutts MJ.** Neutrophil elastase activates near-silent epithelial Na^+ channels and increases airway epithelial Na^+ transport. *Am J Physiol Lung Cell Mol Physiol* 288: L813–L819, 2005.
2. **Cheng SH, Gregory RJ, Marshall J, Paul S, Souza DW, White GA, O'Riordan CR, Smith AE.** Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. *Cell* 63: 827–834, 1990.
3. **Cholon DM, O'Neal WK, Randell SH, Riordan JR, Gentzsch M.** Modulation of endocytic trafficking and apical stability of CFTR in primary human airway epithelial cultures. *Am J Physiol Lung Cell Mol Physiol* 298: L304–L314, 2010.
4. **Collawn JF, Lazrak A, Bebok Z, Matalon S.** The CFTR and ENaC debate: how important is ENaC in CF lung disease? *Am J Physiol Lung Cell Mol Physiol* 302: L1141–L1146, 2012.
5. **Dalemans W, Barbry P, Champigny G, Jallat S, Dott K, Dreyer D, Crystal RG, Pavirani A, Lecocq JP, Lazdunski M.** Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. *Nature* 354: 526–528, 1991.
6. **Dekkers JF, Wiegerinck CL, de Jonge HR, Bronsveld I, Janssens HM, de Winter-de Groot KM, Brandsma AM, de Jong NW, Bijvelds MJ, Scholte BJ, Nieuwenhuis EE, van den Brink S, Clevers H, van der Ent CK, Middendorp S, Beekman JM.** A functional CFTR assay using primary cystic fibrosis intestinal organoids. *Nat Med* 19: 939–945, 2013.
7. **Denning GM, Anderson MP, Amara JF, Marshall J, Smith AE, Welsh MJ.** Processing of mutant cystic fibrosis transmembrane conductance regulator is temperature-sensitive. *Nature* 358: 761–764, 1992.
8. **Devor DC, Singh AK, Bridges RJ, Frizzell RA.** Psoralens: novel modulators of Cl^- secretion. *Am J Physiol Cell Physiol* 272: C976–C988, 1997.
9. **Favia M, Mancini MT, Bezzerri V, Guerra L, Laselva O, Abbattiscianni AC, Debellis L, Reshkin SJ, Gambari R, Cabrini G, Casavola V.** Trimethylangelicin promotes the functional rescue of mutant F508del CFTR protein in cystic fibrosis airway cells. *Am J Physiol Lung Cell Mol Physiol* 307: L48–L61, 2014.
10. **Grove DE, Rosser MF, Ren HY, Naren AP, Cyr DM.** Mechanisms for rescue of correctable folding defects in CFTRΔ F508. *Mol Biol Cell* 20: 4059–4069, 2009.
11. **He L, Kota P, Aleksandrov AA, Cui L, Jensen T, Dokholyan NV, Riordan JR.** Correctors of ΔF508 CFTR restore global conformational maturation without thermally stabilizing the mutant protein. *FASEB J* 27: 536–545, 2013.
12. **Heda GD, Tanwani M, Marino CR.** The ΔF508 mutation shortens the biochemical half-life of plasma membrane CFTR in polarized epithelial cells. *Am J Physiol Cell Physiol* 280: C166–C174, 2001.
13. **Jurkuvenaite A, Chen L, Bartoszewski R, Goldstein R, Bebok Z, Matalon S, Collawn JF.** Functional stability of rescued delta F508 cystic fibrosis transmembrane conductance regulator in airway epithelial cells. *Am J Respir Cell Mol Biol* 42: 363–372, 2010.
14. **Knapp JM, Wood AB, Phuan PW, Lodewyk MW, Tantillo DJ, Verkman AS, Kurth MJ.** Structure-activity relationships of cyanoquinolines with corrector-potentiator activity in ΔF508 cystic fibrosis transmembrane conductance regulator protein. *J Med Chem* 55: 1242–1251, 2012.
15. **Koehler DR, Downey GP, Sweezey NB, Tanswell AK, Hu J.** Lung inflammation as a therapeutic target in cystic fibrosis. *Am J Respir Cell Mol Biol* 31: 377–381, 2004.
16. **Lin S, Sui J, Cotard S, Fung B, Andersen J, Zhu P, El Messadi N, Lehar J, Lee M, Staunton J.** Identification of synergistic combinations of F508del cystic fibrosis transmembrane conductance regulator (CFTR) modulators. *Assay Drug Dev Technol* 8: 669–684, 2010.
17. **Livraghi-Butrico A, Kelly EJ, Wilkinson KJ, Rogers TD, Gilmore RC, Harkema JR, Randell SH, Boucher RC, O'Neal WK, Grubb BR.** Loss of Cftr function exacerbates the phenotype of Na^+ hyperabsorption in murine airways. *Am J Physiol Lung Cell Mol Physiol* 304: L469–L480, 2013.
18. **Lukacs GL, Chang XB, Bear C, Kartner N, Mohamed A, Riordan JR, Grinstein S.** The delta F508 mutation decreases the stability of cystic fibrosis transmembrane conductance regulator in the plasma membrane. Determination of functional half-lives on transfected cells. *J Biol Chem* 268: 21592–21598, 1993.
19. **Ma T, Thiagarajah JR, Yang H, Sonawane ND, Folli C, Galietta LJ, Verkman AS.** Thiazolidinone CFTR inhibitor identified by high-through-

put screening blocks cholera toxin-induced intestinal fluid secretion. *J Clin Invest* 110: 1651–1658, 2002.

20. **Mendoza JL, Schmidt A, Li Q, Nuvaga E, Barrett T, Bridges RJ, Feranchak AP, Brautigam CA, Thomas PJ.** Requirements for efficient correction of ΔF508 CFTR revealed by analyses of evolved sequences. *Cell* 148: 164–174, 2012.
21. **Mills AD, Yoo C, Butler JD, Yang B, Verkman AS, Kurth MJ.** Design and synthesis of a hybrid potentiator-corrector agonist of the cystic fibrosis mutant protein ΔF508-CFTR. *Bioorg Med Chem Lett* 20: 87–91, 2010.
22. **Nicolis E, Lampronti I, Dechecchi MC, Borgatti M, Tamanini A, Bezzerri V, Bianchi N, Mazzon M, Mancini I, Giri MG, Rizzotti P, Gambari R, Cabrini G.** Modulation of expression of IL-8 gene in bronchial epithelial cells by 5-methoxypsoralen. *Int Immunopharmacol* 9: 1411–1422, 2009.
23. **Okiyoneda T, Veit G, Dekkers JF, Bagdany M, Soya N, Xu H, Roldan A, Verkman AS, Kurth M, Simon A, Hegedus T, Beekman JM, Lukacs GL.** Mechanism-based corrector combination restores ΔF508-CFTR folding and function. *Nat Chem Biol* 9: 444–454, 2013.
24. **Pedemonte N, Lukacs GL, Du K, Caci E, Zegarra-Moran O, Galietta LJ, Verkman AS.** Small-molecule correctors of defective ΔF508-CFTR cellular processing identified by high-throughput screening. *J Clin Invest* 115: 2564–2571, 2005.
25. **Pedemonte N, Tomati V, Sondo E, Caci E, Millo E, Armirotti A, Damonte G, Zegarra-Moran O, Galietta LJ.** Dual activity of aminoarylthiazoles on the trafficking and gating defects of the cystic fibrosis transmembrane conductance regulator chloride channel caused by cystic fibrosis mutations. *J Biol Chem* 286: 15215–15226, 2011.
26. **Phuan PW, Yang B, Knapp JM, Wood AB, Lukacs GL, Kurth MJ, Verkman AS.** Cyanoquinolines with independent corrector and potentiator activities restore ΔPhe508-cystic fibrosis transmembrane conductance regulator chloride channel function in cystic fibrosis. *Mol Pharmacol* 80: 683–693, 2011.
27. **Rabeh WM, Bossard F, Xu H, Okiyoneda T, Bagdany M, Mulvihill CM, Du K, di Bernardo S, Liu Y, Konermann L, Roldan A, Lukacs GL.** Correction of both NBD1 energetics and domain interface is required to restore ΔF508 CFTR folding and function. *Cell* 148: 150–163, 2012.
28. **Ren HY, Grove DE, De La Rosa O, Houck SA, Sopha P, Van Goor F, Hoffman BJ, Cyr DM.** VX-809 corrects folding defects in cystic fibrosis transmembrane conductance regulator protein through action on membrane-spanning domain 1. *Mol Biol Cell* 24: 3016–3024, 2013.
29. **Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL, Drumm ML, Iannuzzi MC, Collins FS, Tsui L-C.** Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 245: 1066–1073, 1989.
30. **Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, Rozmahel R, Cole JL, Kennedy D, Hidaka N, Zsiga M, Buchwald M, Riordan JR, Tsui L-C, Collins FS.** Identification of the cystic fibrosis gene: chromosome walking and jumping. *Science* 245: 1059–1065, 1989.
31. **Rowe SM, Miller S, Sorscher EJ.** Cystic fibrosis. *N Engl J Med* 352: 1992–2001, 2005.
32. **Rowe SM, Verkman AS.** Cystic fibrosis transmembrane regulator correctors and potentiators. *Cold Spring Harb Perspect Med* 3: a015677, 2013.
33. **Sharma M, Benharouga M, Hu W, Lukacs GL.** Conformational and temperature-sensitive stability defects of the delta F508 cystic fibrosis transmembrane conductance regulator in post-endoplasmic reticulum compartments. *J Biol Chem* 276: 8942–8950, 2001.
34. **Tamanini A, Borgatti M, Finotti A, Piccagli L, Bezzerri V, Favia M, Guerra L, Lampronti I, Bianchi N, Dall'Acqua F, Vedaldi D, Salvador A, Fabbri E, Mancini I, Nicolis E, Casavola V, Cabrini G, Gambari R.** Trimethylangelicin reduces IL-8 transcription and potentiates CFTR function. *Am J Physiol Lung Cell Mol Physiol* 300: L380–L390, 2011.
35. **Thibodeau PH, Richardson JM 3rd, Wang W, Millen L, Watson J, Mendoza JL, Du K, Fischman S, Senderowitz H, Lukacs GL, Kirk K, Thomas PJ.** The cystic fibrosis-causing mutation deltaF508 affects multiple steps in cystic fibrosis transmembrane conductance regulator biogenesis. *J Biol Chem* 285: 35825–35835, 2010.
36. **Van Goor F, Hadida S, Grootenhuis PD, Burton B, Stack JH, Straley KS, Decker CJ, Miller M, McCartney J, Olson ER, Wine JJ, Frizzell RA, Ashlock M, Negulescu PA.** Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809. *Proc Natl Acad Sci USA* 108: 18843–18848, 2011.
37. **Van Goor F, Straley KS, Cao D, Gonzalez J, Hadida S, Hazlewood A, Joubran J, Knapp T, Makings LR, Miller M, Neuberger T, Olson E, Panchenko V, Rader J, Singh A, Stack JH, Tung R, Grootenhuis PD, Negulescu P.** Rescue of ΔF508-CFTR trafficking and gating in human cystic fibrosis airway primary cultures by small molecules. *Am J Physiol Lung Cell Mol Physiol* 290: L1117–L1130, 2006.
38. **Varga K, Goldstein RF, Jurkuvenaite A, Chen L, Matalon S, Sorscher EJ, Bebok Z, Collawn JF.** Enhanced cell-surface stability of rescued ΔF508 cystic fibrosis transmembrane conductance regulator (CFTR) by pharmacological chaperones. *Biochem J* 410: 555–564, 2008.
39. **Ward CL, Omura S, Kopito RR.** Degradation of CFTR by the ubiquitin-proteasome pathway. *Cell* 83: 121–127, 1995.
40. **Yu GJ, Yoo CL, Yang B, Lodewyk MW, Meng L, El-Idreesy TT, Fettinger JC, Tantillo DJ, Verkman AS, Kurth MJ.** Potent s-cis-locked bithiazole correctors of ΔF508 cystic fibrosis transmembrane conductance regulator cellular processing for cystic fibrosis therapy. *J Med Chem* 51: 6044–6054, 2008.