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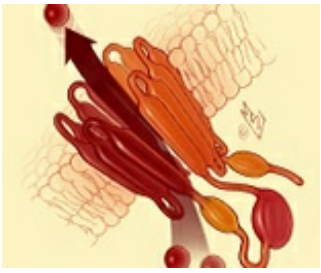

Genotype-Phenotype Correlation and Individualizing Therapy

In this Issue...

ECFS 2017: Authors' Impressions — There was significant attention to new modulator therapies and understanding how modulators and other CFTR therapies are changing the lives of CF patient. In addition, key questions about the effect of modulators on the whole CF phenotype were addressed. Specific highlights and takeaways from this conference include:

- In an excellent seminar session, several new methods for treating CFTR dysfunction in a genotype agnostic approach using DNA or mRNA editing were discussed. While these systems are not ready for clinical trial, they are expected to be useful for a genotype-agnostic approach in rare CFTR variants in the future. Special attention was paid to the CRISPR/Cas9 system for DNA editing.
- In a key workshop, several authors were asked to discuss the potential for modulators to affect the CF lung, endocrine and nutritional phenotype. While all authors concluded that modulators (especially highly effective ones like ivacaftor) improve insulin secretion and lung phenotype, more research is needed to determine if these effects will be large enough and sustained to mitigate the need for other phenotypic treatments like pancreatic enzymes, mucolytics, and insulin.
- In a new therapies workshop, topline data from several key clinical trials was presented. Most notably, the effects of PQ-010, a novel mRNA editing oligonucleotide for Phe508del CFTR, was discussed. The primary endpoint of this proof of concept trial was improved chloride conductance measured using nasal potential difference (NPD). In addition, disappointing results of the PTC-123 study were released demonstrating failure of this read-through agent to improve CFTR function and clinical outcomes.

In this issue, Drs. George Solomon and Bryan Garcia from the University of Alabama at Birmingham review the recent literature (and data newly presented at ECFS 2017) describing how new insights into CFTR mutations, research into biomarkers, and a “theratype” approach—based on understanding a mutation’s specific molecular mechanisms—are helping develop individualized therapies for patients with cystic fibrosis.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Explain the role of new *CFTR* mutation-specific therapies
- Describe how new biomarkers can influence our understanding of disease severity and response to therapies
- Summarize the concept of theratyping

GUEST AUTHORS OF THE MONTH

Commentary & Reviews

Guest Faculty Disclosure

Dr. George Solomon has

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Dr. Bryan Garcia has indicated he has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of this presentation.

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The authors indicate there will be no there will be no references to the unlabeled or unapproved use of any drugs or products.

IN THIS ISSUE

COMMENTARY

Cystic fibrosis (CF) is a recessive genetic disease caused by >1900 mutations in the cystic fibrosis transmembrane conductance regulator protein (CFTR). The manifestations of CF are protean, and the trajectory of sinopulmonary disease is paramount in the long-term prognosis of the disease.[1] The treatment of CF has focused on symptomatic management of the nutritional and sinopulmonary manifestations of the disease. Recently, the discovery of ivacaftor for a particular subset of patients established the concept of individualized therapy, based on the patient's genotype .[2] This treatment modality was also notably linked to large improvements in sweat chloride and other biomarkers of CFTR function.

This current treatment paradigm arose from a well-established scheme that groups CFTR genetic mutations into various defects, including: reduced protein synthesis (class 1 mutations), abnormal protein maturation and folding (class II mutations), abnormal pore opening and gating (class III), and a host of milder forms of protein maturation and conductance defects (classes IV-VI).[3] Most of the milder CF phenotypes, especially pancreatic sufficiency, are found in patients with class IV-VI mutations. In addition, patients with at least one mutation from milder classes often have later age onset of sinopulmonary symptoms.

Differences in the severity of CFTR mutations are thought to be determined by differences in the level of CFTR function. Biomarkers of CFTR, including sweat chloride measurements and nasal potential difference (NPD),[4] have established the level of CFTR function based on genotype, on a spectrum from normal CFTR function to severe defects (ie, increasing levels of sweat chloride). These levels correspond well to the severity of the CFTR mutation defect.[5]

The recent work by Collaco and colleagues (reviewed herein) demonstrates that variation in sweat chloride values are due more to the CFTR mutations present than environmental and/or random factors. This seminal study affirms that we can reasonably expect sweat chloride values to predict genotype and phenotype severity accurately. Future investigation should continue to establish whether the response to disease modifying therapies is best predicted by a highly sensitive biomarker of CFTR function. However, refinements are needed in the assay to account for non-disease state variation (especially environmental influences).

This current scheme of mutation classes has proved quite useful for exploring disease severity and designing strategies for individualized treatment of mutation and mutation classes. In this issue we review the landmark Traffic and Transport trials led by Wainwright et al, which reported a modest improvement in FEV_1 and BMI in patients with Phe508del homozygous mutations after treatment with lumacaftor/ivacaftor. A recent post-hoc analysis by Elborn (also reviewed) established that this response is similar across pulmonary disease severity, suggesting that effective modulation of Phe508del CFTR is possible regardless of initial pulmonary phenotype. Further, the PROGRESS study has recently demonstrated sustainability of lumacaftor/ivacaftor in this patient population over 24 additional weeks of open-label extension therapy. This study prominently identified a 42% reduction of rate of decline of FEV1 compared to historical CFF registry controls.[6]

These trials established several concepts in the developmental process of treatments for Phe508del-CFTR: that the improvements in lung function were more modest than seen in the clinical trials investigating ivacaftor for *G551D*, and that clinical improvements correlated to the mean improvement in the sweat chloride, in aggregate. However, sweat chloride improvements for lumacaftor/ivacaftor were significantly lower than the response seen in G551D patients treated with ivacaftor. Thus, sensitive biomarkers, like reduction in sweat chloride, may predict the response of CFTR modulators on clinical outcome in this genotype class. Also, other recent trials have demonstrated that small reductions in sweat chloride (-11.8 mmol/L) were not associated with improvements in percent predicted FEV_1 in patients heterozygous for Phe508del-CFTR.[7] Since these reductions in sweat chloride are similar to the observations in Phase 2 trials in Phe508del homozygous patients, the sensitivity of this biomarker is challenged. Overall, these studies investigating different mutation classes indicate that sufficient improvement in CFTR is necessary to improve key clinical endpoints.

In this issue, we also review the concept of treating an overlap mutation, R117H-CFTR, which has properties of both abnormal conductance and gating. In the trial by Moss and

colleagues, patients were treated with ivacaftor monotherapy for the gating defect. While sweat chloride declined, in aggregate patient clinical outcomes like lung function failed to improve. However, the authors concluded that this was due to inclusion of patients with milder lung disease (<18 years). This study thus highlights that phenotype determines treatment response, as only patients with more severe established disease experienced improved lung function.

While the concept of mutation classes accurately predicts severity of the disease and is reflected in common biomarkers, recent evidence (reviewed in this issue) by Sabusap et al calls into question the rigidity that may be applied to the current classification scheme for predicting the molecular defect, especially in rare mutations. In this paper, a rare mutation, P67L-CFTR that was previously classified as a conductance mutation, is effectively reclassified using advanced molecular phenotyping. Using these techniques the authors assert that mutations may have more complex molecular mechanisms, and show that treatment of the newly identified mechanism (abnormal processing and gating upon reclassification of *P*67L-CFTR) can be treated in primary human epithelial cells. This paper effectively challenges the notion that molecular mutation classification is the only means to approach personalized therapy in CF.

The Sabusap paper, as well as differential effects seen in various pulmonary phenotypes of R117H-CFTR patients reported by Moss, points to the need to consider a means of theratyping patients rather than relying on their mutation classification alone. In this concept, patients are treated for response using biomarkers, rather than basing therapy on mutation. Thus the concept is built on the notion that we can pair individual responses of a patient's unique genoptype with known CFTR therapies to effect highly individualized therapies for all patients. This concept is particularly appealing in rare mutations where traditional approval studies are logistically challenging.

To move personalized therapeutics forward, biomarkers are key to assessing the level of CFTR function present—to predict severity of illness and especially response to therapy. As current biomarkers do not adequately predict all clinical outcomes in response to therapies, new biomarkers that are suitable for personalized medicine are necessary. In a landmark paper reviewed in this issue, Dekkers et al demonstrate the capacity for rectal organoid cells to predict clinical response to therapy. The capacity for intestine derived tissues to predict pulmonary response and response to traditional biomarkers (eg, sweat chloride or nasal potential difference) will have to be borne out in prospective trials. In addition, simplified means to use these biomarkers will require investigation to permit use in the large research community.

In summary, as the content of this newsletter issue describes, the goal of individualizing therapy for patients with CF is rapidly becoming more focused. As research continues to identify new biomarkers and better clarify how they can predict clinical response, the search for more effective therapies can move beyond the limitations of mutation classification—bringing us toward a new paradigm where we can tailor individual treatment for each patient.

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Lumacaftor–Ivacaftor in Phe508del-CFTR

Wainwright CE, Elborn JS, Ramsey BW, et al; TRAFFIC Study Group; TRANSPORT Study Group. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N Engl J Med.* 215 Jul 16; 373(3):220-31

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Addressing the underlying cause of CF disease by targeting the CFTR protein dysfunction specific to the mutation is a novel example of personalized medicine. The Phe508del-CFTR mutation (also referred to as dF508, deltaF508, or F508del) is the most common CF mutation and results in improper protein folding and abnormal gating. For this reason, correction of this protein is thought to require two steps. The CFTR corrector molecule, VX-809 (lumacaftor) has been shown to correct Phe508del-CFTR misprocessing and increase the amount of cell surface-localized proteins. VX-770 (ivacaftor) potentiates CFTR gating activity in patients with the G551D mutation. Although neither VX-770 nor VX-809 alone has been shown to augment CFTR activity in the Phe508del mutation, the combination of these compounds has been shown *in vitro* to increase the number of dF508-CFTR channels at the epithelial membrane surface and augment functionality of these channels on reaching the cell surface.

This article provides positive results from two phase-3 clinical trials, TRAFFIC and TRANSPORT, which evaluated the efficacy and safety of two doses of lumacaftor in combination with ivacaftor in patients with cystic fibrosis who were homozygous for the Phe508del CFTR mutation. The studies were identically designed multinational, randomized, double blind, placebo-controlled, parallel-group studies. Patients were randomly assigned (in a 1:1:1 ratio) to one of three study groups: 600 mg of lumacaftor once daily in combination with 250 mg of ivacaftor every 12 hours, 400 mg of lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours, or placebo every 12 hours. Randomization was stratified according to age (<18 years vs ≥18 years), sex, and pulmonary function (percentage of predicted FEV_1 at screening, <70% vs. ≥70%). The primary end point was difference in FEV_1 percent predicted between the treatment groups and the placebo group.

At 24 weeks, a significant improvement was observed in mean absolute change in FEV_1 percent predicted in the lumacaftor/ivacaftor treatment groups in both studies, ranging from 2.6 to 4.0 percentage points (P<.001 for all comparisons). In addition, clinically significant reductions in pulmonary exacerbations, hospitalizations, and use of IV antibiotics was identified across all treatment groups compared to placebo. A statistically significant improvement in CFQ-R scores was seen across treatment groups and treatment resulted in improved nutritional status (BMI) in the TRANSPORT study.

Treatment was well tolerated and side effects were generally mild. Dyspnea and chest tightness were the most common side effects reported, and these symptoms resolved after two to three weeks of treatment in those who did not discontinue therapy. Although a higher proportion of patients in the treatment arms had elevated liver function tests, this resolved upon discontinuation of therapy.

This article presents the landmark findings for the use of a CFTR corrector and potentiator in combination for the treatment of patients homozygous for the most common (Phe508del) CF mutation. Significant clinical improvements in lung function, nutritional status, and decreased exacerbation frequency were identified in patients receiving combination lumacaftor-/ivacaftor therapy.

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Lumacaftor/Ivacaftor: Efficacy and Safety by Pulmonary Function Subgroup

Elborn JS, Ramsey BW, Boyle MP, at al; VX-809 TRAFFIC and TRANSPORT study groups. Efficacy and Safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup. Lancet Respir Med 2016; 4: 617-626

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The Traffic and Transport studies provided the first evidence for efficacy of CFTR modulation in homozygous patients with the Phe508del mutation. T he authors sought to determine the differential effect on the primary endpoint (absolute change in $FEV_{1\ percent\ predicted}$) in patients with severe (FEV_1 <40% and ≥40%) and mild (<70% or ≥70%) lung function impairment. In this study, 1108 patients received at least one dose of lumcaftor/ivacaftor at two efficacious doses (ivacaftor 250 mg twice daily plus lumacaftor either 400 mg twice daily or 600 mg daily). The difference in effects of treatment in each of these lung function severity groups with regard to relative change in $ppFEV_1$, relative increase of ≥5% $ppFEV_1$, as well as absolute change in BMI and symptoms (CFQ-R, respiratory domain) were also assessed in a post-hoc analysis.

Of the 1108 patients, 81 patients had a FEV_1 percent predicted that had decreased to <40% from screening to baseline and were analyzed in this group. Most patients (730, 66%) had a lung function of FEV_1 <70%. There were statistically significant improvements in absolute and relative FEV_1 percent predicted in all four groups, although the magnitude of improvement was reduced in the group with FEV_1 percent predicted ≥70%, as expected (P =.079 for the group who received lumacaftor 400 mg twice daily). Surprisingly, the patients with FEV_1 <40% demonstrated absolute changes of FEV_1 percent predicted similar to those in patients who had FEV_1 >40%. All subgroups analyzed were more likely to have large responses in FEV_1 (>5% to 10% relative increase above baseline) except for the subgroup of patients with FEV_1 <40%.

Nutritional parameters, especially absolute improvement in BMI at 24 weeks of treatment, improved in all patient groups. While there was significant variability in symptoms score, the CFQ-R significantly improved in all groups except for the patients with $ppFEV_1$ <40%. This group had notably higher adverse pulmonary events, especially abnormal respiration (chest tightness) which associated strongly with treatment in the severe lung function group. Since these events were of particular concern, it may mitigate the benefit of this drug in a particular sick group already susceptible to pulmonary symptoms. Clinicians must individualize their approach to each patient treated in this group.

In summary, this post-hoc analysis provides further evidence that patients across nutritional and pulmonary disease spectra will benefit from CFTR modulation.

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Ivacaftor and Arg117His

Moss RB, Flume PA, Elborn JS, et al; VX11-770-110 (KONDUCT) Study Group. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. Lancet Respir Med. 2015 Jul;3(7):524-533.

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Five percent of CF patients have the G551D mutation, a class III gating mutation that results in significant pulmonary and gastrointestinal disease but is a clinical phenotype that is typically less severe than the PheF508del mutation. The novel CFTR potentatior, VX-770 (ivacaftor), has been shown to provide significant clinical improvements in patients with the G551D mutation, including augmented pulmonary function (FEV_1 percent predicted) and nutritional status/BMI.

Similar to the G551D mutation, R117H is a class III/IV combined gating and conductance mutation, resulting in moderately conserved CFTR activity and thus a less severe clinical phenotype. Prior to the advent of newborn screening, patients with this mutation were historically diagnosed at an older age. Patients with this mutation are typically pancreatic sufficient. As described in this paper, the effect of this mutation on disease phenotype is more complex than other CFTR mutations, due to the effect of a *cis*-localized intron 8-polythymidine (Poly-T) tract which effects proper splicing of CFTR mRNA transcripts. The three common alleles at the Poly-T locus (5T, 7T, and 9T) occur with varying geographic frequency, with the 5T variant associated with greatest risk for disease severity.

Prior to this study, the effect of the CFTR potentiator ivacaftor on non-G551D class III gating mutations had been theorized and case reports had described clinical success. This study presents the results of a 24-week, double blind, placebo controlled randomized control trial which evaluated the efficacy of ivacaftor in 69 CF patients with the R117H mutation with a percent predicted FEV_1 percent predicted ≥40%, followed by a 12-week washout period and culminating with an open-label extension study.

After 24 weeks, treatment with ivacaftor improved FEV_1 percent predicted (ivacaftor [n=34] and placebo [n=35]) by 2.1 percentage points across all patient ages; however, these results failed to reach statistical significance (P =.20). Despite this, in a pre-specified subgroup analysis, FEV_1 percent predicted did significantly improve with ivacaftor in subjects aged ≥18 years (treatment difference versus placebo: 5.0 percentage points; P=.01), but not in subjects aged 6 to 11 years (–6.3 percentage points; p=0.03). This finding was thought to be due to a ceiling effect as the younger participants had well preserved lung function at the onset of this study. No significant change in nutritional status was identified, and there was a low incidence of hospitalization or the use of IV antibiotics across all groups.

These findings were likely due to a pre-existing residual CFTR function among these patients, resulting in a patient population with less severe disease and infrequent pancreatic insufficiency compared to patients with more severe genotypes (including the G551D and dF508), for whom these outcomes are better indicators of response to therapy. In conjunction with this finding, patients with greater risk of CF disease, including those with the 5T variant, demonstrated more frequent and greater clinical response (FEV_1 percent predicted) to ivacaftor than those with 7T.

Given the clear association with residual CFTR activity and improved clinical course, recent articles have suggested that pulmonary function and BMI alone will be insufficient measures of response to CFTR modulatory therapy. For this reason, sweat chloride and CFQ-R, a validated CF-related quality of life questionnaire, have been utilized as additional means to assess treatment efficacy. In this study, patients receiving ivacaftor demonstrated improvements in both sweat chloride (–24.0 mmol/L; P <.001) and CFQ-R respiratory domain (8.4; P=.009). Although the magnitude of decrease of sweat chloride in this study was less than that achieved in the G551D study, treatment with ivacaftor in patients with the R117H mutation was associated with lowering of sweat chloride to levels below the threshold for CF diagnosis.

In summary, this study provides new data demonstrating the important relationship between genotype and phenotypic response to treatment in the era of CFTR modulators. Although the primary endpoint of pulmonary function across all patients was not met, CFTR activity was

augmented (as demonstrated by the improved sweat chloride) and this may provide long-term stability of pulmonary function if started at a young age, prior to progressive respiratory failure. Furthermore, treatment with VX-770 in patients with the R117H mutation resulted in augmented pulmonary function. Further evaluation of the effect of the cis-poly T locus and response to treatment is needed and will provide further insight on the effect of genotype and phenotypic response to treatment.

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Sweat Chloride Variability

Collaco JM, Blackman SM, Raraigh KS, et al. Sources of Variation in Sweat Chloride Measurements in Cystic Fibrosis. *Am J Respir Crit Care Med*. 2016 Dec 1; 194(11): 1375-1382.

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Sweat chloride is a key *in vivo* biomarker for the diagnosis of CF and monitoring of CFTR therapeutic interventions. Biomarkers of CFTR functional level are important as they correlate to disease status, especially pancreatic/nutritional (pancreatic sufficiency) and pulmonary status. Because of the importance of sweat chloride in both research and in the care of CF patients, Collaco et al sought to determine whether CFTR genotype is the key determinant of sweat chloride variation in a large cohort of CF patients and their siblings.

Analyzing 2768 sweat chloride samples from the CF Twin-Sibling study (as well as two other large databases) by a mixed models analysis method, the authors sought to determine the statistical importance of CFTR genotype, demographics, random biological/environmental factors, and non-CFTR gene modifiers in determining variation in repeated and single measures of sweat chloride. Among the findings:

- In a linear regression of demographic variables, including age, sex, and ethnicity, the authors noted significant increases in sweat chloride with age and trends for higher values in males, as well as a non-significant contribution of ethnicity. Because most subjects were <5 years old, the long-term effect of sweat chloride (eg, linear nature of increase) cannot be assessed from this study. Thus, indeterminate sweat chloride testing in adult patients may remain a challenge for diagnosis.
- A nested mixed model analysis demonstrated that ~60% of the variation of sweat chloride is attributable to CFTR genotype alone, with other factors including variation in testing days and modifier genes. In this mixed mixed age- controlled model, variations in time (different days of testing), random environmental factors, and unique individual modifiers accounted for the remaining ~40% of variation.
- A twin study of Phe508del patients allowed assessment of the effect of known CFTR modifier genes. In this heritability analysis, variability between mono and di-zygotic twins is almost identical, indicating that modifier gene variability does not account for the differences in sweat chloride. This finding suggests that CFTR genotype is the key determinant of sweat chloride, although electrolyte transport genes in the sweat gland may emerge as future candidates.

In summary, this study provides a deeper understanding of the sources of variability in a key CFTR biomarker. Clearly the severity of gene defect accounts for much of the variation of sweat chloride values across patients. However, accounting for differences in environmental and testing variability remain challenges to using this biomarker across the disease spectrum.

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Personalized Therapeutics: P67L-CFTR

Sabusap CM, Wang W, McNicholas CM, et al. Analysis of cystic fibrosis–associated P67L CFTR illustrates barriers to personalized therapeutics for orphan diseases. *JCI Insight.* 2016;1(14):e86581.

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Apart from the most common severe mutations (majority Phe508del), >1900 disease-causing mutations in CFTR have been identified. As some of these may cause disease in only a small proportion of patients, investigating the effect of CFTR modulators is difficult through routine clinical trial testing. Understanding the complexities of molecular classification of uncommon mutations has brought about interest in theratyping of patients along the lines of response to therapeutics.

In this recent article, Sabusap and colleagues reexamine the concept of mutation class and theratyping with respect to the rare gene variant *P67L*. This mutation has been described as causing a milder CF phenotype, with pancreatic sufficiency and later onset of symptoms, a phenotypic difference partially explained by classifying *P67L* as a mild “conductance” (class IV) mutation. Furthermore, previous work has demonstrated some responsiveness to ivacaftor in patients with *P67L,* suggesting some theratyping possibilities for this rare mutation.

The investigators used a diverse set of techniques to clarify the molecular phenotype of this unique mutation. In particular, they found that *P67L* displays a complex molecular mechanism resulting in defective function. First, the authors demonstrated reduced mature protein biogenesis and demonstrated in a cell model improved formation of mature CFTR after the addition of the corrector molecule lumacaftor. In addition, the authors examined the pore characteristics of P67L-CFTR in cell models and found that the pore displays normal conductance, and thus is not emblematic of a class IV mutation. Rather, the investigators show that the mutation instead demonstrates reduced open probability, signifying that it has a gating defect. The authors confirmed that a theratyping approach similar to Phe508del CFTR with co-treatment of lumacaftor/ivacaftor. Primary human airway cells demonstrated improved CFTR-dependent activity with simultaneous correction and potentiation of *P67L CFTR*.

In summary, this article demonstrates that precise molecular phenotyping of CFTR mutations helps to establish a new paradigm for precise intervention for CFTR modulation. The authors use an emblematic example to challenge the paradigm that the molecular classification of mutations is precise enough to predict response to novel therapeutics. This concept will enable a move towards theratyping of individual mutations as a means to achieve precision therapeutics for CF patients.

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Measuring CFTR Response by Rectal Organoids

Dekkers JF, Berkers G, Kruisselbrink E, et al. Characterizing responses to CFTR-modulating drugs using rectal organoids derived from subjects with cystic fibrosis. *Sci Transl Med.* 2016 Jun 22;8(344):344ra84.

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While conducting clinical trials for all patients with rare mutations would be expensive, time consuming, and in some cases logistically impossible, these individuals may still benefit clinically from current and emerging therapeutics designed to restore or augment CFTR function. This 2016 report describes the use of rectal derived organoid cultures as a model for both evaluating the in vitro efficacy of new CFTR therapies and to predict clinical response by patients with common as well as rare CFTR mutations.

Rectal organoids are three dimensional primary stem cell cultures that self-organize into tissue re-capitulating “mini-guts”. The authors describe the development of two new assays: a forskolin induced swelling assay (FIS) as a sensitive means of measuring CFTR response to modulator therapies, and a steady state lumen area assay (SLA) to compare cellular response to CFTR potentiator or modulator therapies.

The strength of this paper lies in the authors’ access to rectal organoids from patients with the G551D and Phe508del/Phe508del mutations who have received ivacaftor or ivacaftor-/lumacaftor. The investigators demonstrated a strong correlation between organoid response to these compounds (evaluated using the FIS and SLA assays) and the patients’ previously known clinical responses. These findings serve as evidence in favor of using rectal organoids to predict patient specific clinical response to future CFTR augmentation therapeutics.

As additional proof of concept, the authors selected two patients with a rare CFTR genotype (G1249R/F508del) for treatment with ivacaftor based on response by these patients' rectal organoids to the FIS and SLA assays. The patients showed FIS and SLA within the expected range for clinical response, and in fact demonstrated improvements in sweat chloride, body mass index, and pulmonary function. Another patient with the genotype F508del/R347P whose organoids demonstrated a relatively weak response to ivacaftor, when treated failed to show improvements in sweat chloride, nasal potential difference, or pulmonary function.

While this article provides evidence for a novel method of predicting clinical response to CFTR augmentation, it is important to note that at present these assays remain unlikely to obtain more widespread use due to the expertise required to obtain, harvest, differentiate, and maintain this system.

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KEY TAKEAWAYS

- New FDA labeling studies of lumacaftor/ivacaftor have increased the available CFTR modulator pool and extended this therapeutic class to a larger set of patients.
- New understanding of biomarkers holds promise for individualizing therapies—especially extending the indications of currently approved therapies.
- Molecular techniques paired with these new biomarkers can tell us a great deal about theratyping of modulator therapies to individual patients.

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