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No TWEAK for COPD

To the Editor:

The therapy with the greatest functional benefit in chronic obstructive pulmonary disease (COPD) is pulmonary rehabilitation [1]; while the mode of action is probably multifactorial the functional benefit of pulmonary rehabilitation is associated with strength gain in the quadriceps [2]. This suggests that muscle hypertrophy, or countering atrophy, could be at least one of the mechanisms through which pulmonary rehabilitation is beneficial. However, despite the success of pulmonary rehabilitation, there are several occasions in which an effective adjunctive drug therapy might have a place in clinical practice; for example in patients who are too unwell to exercise, in patients unwilling or unable to complete pulmonary rehabilitation, or indeed to magnify or extend benefit in those who do.

In order to conduct stratified medicine studies of future novel anabolic agents for skeletal muscle dysfunction in COPD, biomarkers to identify potential responders will be required. In particular, it is likely that such therapies may be aimed at subsets of patients with COPD rather than, as is the case with most current therapies, targeted at all patients with the condition. In the case of a novel anabolic agent, it is likely that those with skeletal muscle weakness, which is present in ~30% of patients [3, 4], would benefit most and, therefore, should be the subgroup in which a study would be conducted [5].

TNF-like weak inducer of apoptosis (TWEAK, TNFSF12) is an inflammatory cytokine which is a member of the tumour necrosis factor (TNF) superfamily. When chronically overexpressed in a murine model, TWEAK has been reported to cause skeletal muscle wasting through upregulation of E3 ubiquitin ligases [6]. Few data in

TABLE 1 Characteristics for sTWEAK subjects

	COPD			Controls		
	ECLIPSE	**RBH**	**Combined**	**ECLIPSE**	**RBH**	**Combined**
Subjects n	90	114	204	24	30	54
Age years	62.5 ± 7.5	66.4 ± 8.1	64.7 ± 8.1	62.0 ± 8.9	67.1 ± 7.7	64.8 ± 8.5
Males %	63.3	66.7	65.2	50.0	53.3	51.9
Current smokers %	40.0	18.9	28.4	8.3	6.7	7.4
BMI kg·m^{-2}	25.8 ± 5.45	24.2 ± 4.82	25.1 ± 5.13	26.8 ± 4.30	26.1 ± 4.18	26.4 ± 4.21
FFMI kg·m^{-2}	13.2 ± 5.46	16.0 ± 2.18	14.2 ± 4.20	14.1 ± 4.94	17.2 ± 2.36	15.8 ± 4.02
FEV1 L	1.22 ± 0.44	1.11 ± 0.52	1.16 ± 0.49	3.02 ± 0.62	2.85 ± 0.64	2.93 ± 0.63
FEV1 % pred	43.8 ± 14.59	42.6 ± 19.21	43.2 ± 17.31	111.2 ± 15.22	109.2 ± 13.54	110.1 ± 14.20
FVC L	3.21 ± 0.90	3.18 ± 0.96	3.19 ± 0.93	3.92 ± 0.79	4.03 ± 0.87	3.98 ± 0.83
FVC % pred	91.6 ± 18.41	92.8 ± 20.53	92.3 ± 19.59	117.2 ± 16.29	122.5 ± 18.86	120.1 ± 17.80
6MWD m	386 ± 127	385 ± 123	386 ± 124	ND	600 ± 86	600 ± 86[#]
QMVC kg	33.2 ± 13.25	29.7 ± 10.14	31.2 ± 11.72	41.3 ± 11.63	34.9 ± 9.67	37.8 ± 10.97
sTWEAK pg·mL^{-1}	825.84 (236.67)	834.17 (286.50)	828.34 (276.25)	821.67 (115.00)	826.67 (98.67)	826.00 (105.08)

Data are presented as mean $\pm$ SD or median (interquartile range), unless otherwise stated. sTWEAK: soluble tumour necrosis factor-like weak inducer of apoptosis; COPD: chronic obstructive pulmonary disease; ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; RBH: Royal Brompton Hospital; BMI: body mass index; FFMI: fat-free mass index; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; 6MWD: 6-min walk distance; QMVC: quadriceps maximum voluntary contraction; ND: not done. [#]: RBH controls only.

patients with COPD exist but, in data thus far only available in abstract form [7], levels of soluble TWEAK (sTWEAK) were reported to be increased in a cohort of COPD patients with muscle weakness. sTWEAK, in the presence of inflammation, is associated with increased mortality among patients with renal failure [8] and, in some patients with COPD, upregulation of TNF has been reported to drive skeletal muscle dysfunction [9]. We therefore hypothesised that sTWEAK might be a useful biomarker of skeletal muscle dysfunction in COPD.

To test this hypothesis, levels of sTWEAK were measured in a convenience sample of 90 COPD subjects and 24 control subjects from the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort (www.eclipse-copd.com, NCT00292552, GSK Study No. SCO104960) [10], in whom muscle strength had been measured [11], and 114 COPD subjects and 30 control subjects studied as part of another investigation performed at the Royal Brompton Hospital, London, UK [12], giving a combined total of 204 COPD subjects and 54 control subjects (table 1). In both cases, written consent provided by the patients provided for the testing of surplus serum for possible novel biomarkers of disease. Serum sTWEAK was measured using an immunoassay validated for use with serum samples (R&D Systems, Inc., Minneapolis, MN, USA). Core measurements in both datasets included age, weight, fat-free mass by bioimpedence, isometric quadriceps maximum voluntary contraction force and the 6-min walk distance conducted according to American Thoracic Society/European Respiratory Society guidelines except that a practice walk was not undertaken in ECLIPSE; further methodological details may be found in the primary manuscripts.

Data are shown in table 1; in the combined COPD subjects, serum sTWEAK levels were similar to those seen in the combined control subjects. Serum sTWEAK levels were also similar in COPD and control subjects within each of the individual studies. In paired samples collected from the ECLIPSE subjects, separated by 1 year, sTWEAK levels were broadly reproducible (data not shown). However, at a cross-sectional level no relationships were observed between serum sTWEAK and the following measures: quadriceps maximal voluntary contraction force, 6-min walk (whether expressed as per cent predicted or in metres) or fat-free mass index considered either alone or stratified by age, sex or smoking status.

Despite the use of two cohorts and a large sample size, we do acknowledge that some scenarios were not tested in the present study. In particular, sTWEAK was not measured in patients during acute exacerbation, in response to rehabilitation or at different times of the day. Nevertheless our prediction from the current data is that such studies are unlikely to be fruitful.

In summary, we observed no relationships between sTWEAK and quadriceps strength, fat-free mass or exercise performance. Since these variables have all also been reported as predictors of mortality it seems unlikely that, in patients with COPD, sTWEAK would predict mortality either. The available data suggest that sTWEAK will not be a useful biomarker in COPD associated skeletal muscle weakness.

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Genome-wide genetic ancestry measurements to predict lung function in European populations

To the Editor:

A number of models have been proposed to predict spirometric lung function using age, sex, height and self-reported ethnicity [1, 2]. These models are particularly important to derive per cent predicted lung function and establish the severity of lung diseases such as chronic obstructive pulmonary disease (COPD) [3]. Compared to self-reported race and/or ethnicity, genetic data can provide more accurate and objective measurements of ancestry and has the potential to alleviate some of the problems related to the lack of consensus on the definition of race and ethnicity worldwide [4]. A recent report suggested that genetically determined ancestry improves predicted lung-function measurements in African Americans [5]. Here, we