**Inhaled GSH tolerability in patients with cystic fibrosis (CF)**

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**Objectives:** Oxidative stress biomarkers as reactive oxygen species are induced by GSH. Patients with CF disease and exposed to GSH inhalation test (10mg/kg, maximum dosage 600mg/dose) to evaluate inhaled GSH in cohort of CF patients. We report preliminary data on tolerability to GSH in pediatric subset of enrolled patients.

**Methods:** 48 CF patients (F 23, age M ± SD: 3.5 ± 5.9 years), in regular follow up at the Regional Pediatric CF Center of Naples, were enrolled for CRT. The main inclusion criteria were: CF diagnosis by sweat test and/or two CF causing mutations, age of patients ≥6 years, FEV1% >40% of the predicted value, negative culture for *Burkholderia cepacia*. Spirometry was performed before and 10 minutes after GSH inhalation test (10mg/kg, maximum dosage 600mg/dose) in order to assess tolerability.

**Conclusions:** No patients showed a decrease in FEV1% >15% after GSH inhalation as defined in the study design. A statistically significant increase was observed in both T0 71.64 ± 32% and T60 35.25 ± 32%, p < 0.0001 for FEV1% after 60 minutes from inhalation (FEV1 M ± SD: T0 97.90 ± 21.03 VS T60 100.01 ± 19.42; p < 0.01). No side effects were reported. On the basis of these preliminary results we are currently evaluating the efficacy of inhaled GSH on pulmonary function and inflammatory markers within a 12 months therapy.

**Nebulized hyaluronan ameliorates lung inflammation in cystic fibrosis (CF) mice**

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**Objectives:** Chronic lung inflammation and bacterial infections cause much of the morbidity and mortality in patients with CF. Previous studies have shown that hyaluronan (HA) may exert a protective effect against injury in experimental models of chronic respiratory diseases. Our objective was to examine if exogenous administration of nebulized HA might interfere with lung inflammation in vivo in mouse models of CF.

**Methods:** F508del homozygous mice (CftrF508del) and transgenic mice overexpressing the ENaC channel (β-subunit (Snn1b-Tg)) were treated with nebulized HA (0.5 mg per animal in saline solution for 30 minutes once daily for 7 days). TNFα expression, MIP2 levels, MPO activity and macrophage infiltration were assessed on lung tissues. CF cell lines were cultured with HA (24h, 100µg/ml) and Reactive Oxygen Species (ROS), Tissue Transglutaminase (TG2) SUMOylation, PPARγ and phospho-p42/p44 levels were measured by dichlorofluorescein assay, or FRET microscopy or immunoblots.

**Conclusions:** Nebulized HA reduced TNFα mRNA levels (52±30%, and 64±32%, p < 0.005), MIP2 (56±9% and 79±7%, p < 0.05), MPO protein levels (from 1.780.47±0.973.18 to 548.843.386.64 and from 2325.25±840.83 to 1003.12±722.13 nmol/min/ml, p < 0.05), CDE8 ± cells counts in lung tissues (from 102.4±27.1 to 36.6±19.2 and from 62.4±28.2 to 25.8±13.2 per mm² of tissue, p < 0.005) in both Cfrtf508del and Snn1b-Tg mice, respectively, as compared to saline-treated mice. HA reduced ROS, TG2 SUMOylation, TG2 enzyme activity, phospho-p42/p44 and increased PPARγ protein in both IB3−1 and CFBE41o− cell lines (p < 0.05). Inhaled HA could be effective as a potential anti-inflammatory drug in CF therapy.