Small molecule inhibitors of JAK1/2 improve physiological and functional measures of cancer-associated cachexia

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ABSTRACT # 2848

Cancer-associated cachexia (CAC) is a significant contributing factor to the morbidity and mortality of malignancy. Though poorly defined, CAC is broadly described as a significant unintended and undesirable weight loss often accompanied by fatigue, altered metabolism, and systemic inflammation. Here, we attempt to understand the role of inflammation in CAC and demonstrate that IL-6, amongst other cytokines, contributes to multiple aspects of cachexia. Furthermore, we show that pharmacological antagonism of inflammatory cytokine signaling - via inhibition of JAK1/2 - reduces aberrant JAK/STAT activity and dramatically improves body mass and physical performance in mouse models of CAC.

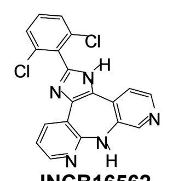
We characterized CAC using 3 tumor models (Colon26, PC-3M, and A375.S2). Effects of tumors on body weight ranged from total inhibition of weight gain to ≥30% weight loss; muscle and fat were depleted with a maximum loss of ~90% of parametrial fat stores and ~50% of gastrocnemius muscle weight. These changes had a dramatic effect on physical performance as demonstrated by decrements in grip strength and locomotor activity approaching 50% and 90%, respectively. Splenomegaly was observed in the majority of models suggesting systemic inflammation may contribute to the cachectic state. We therefore performed an unbiased analysis of plasma samples from cachectic mice and identified a number of markedly elevated inflammatory cytokines and chemokines, many of which signal through the non-receptor tyrosine kinases JAK1/2 (e.g. IL-6, IL12, and IL17) or which are indirectly stimulated by such cytokines (e.g. IL-6 induced MCP-1). Moreover, administration of physiologically relevant levels of IL-6 was sufficient to activate JAK/STAT in muscle and result in reduced lean body mass and grip strength. Because of the reported and observed inflammatory components of CAC, we hypothesized that pharmacological inhibition of JAK1/2 may prevent or improve the cachectic phenotype. Using selective inhibitors (INCB16562 and INCB19408), we demonstrated that systemic inhibition of JAK1/2 reduces aberrant JAK/STAT signaling in muscle in the aforementioned models, minimizes splenomegaly and has a marked tissue salvaging effect on both fat and muscle resulting in striking functional improvements (~200%) in strength and activity. These effects were not associated with changes in food consumption or tumor growth. In summary, the data suggest that multiple JAK-activating cytokines are elevated in CAC and contribute to functional deficits associated with the condition. Moreover, we show that systemic inhibition of JAK1/2 can reduce inflammation, improve total and lean body mass, and enhance functional performance in multiple cachexia models. Clinical exploration of selective JAK inhibition is therefore warranted for the prevention or alleviation of CAC.

1. Biochemical and cellular characterization of Incyte JAK inhibitors

Kinase Potency* (nM)

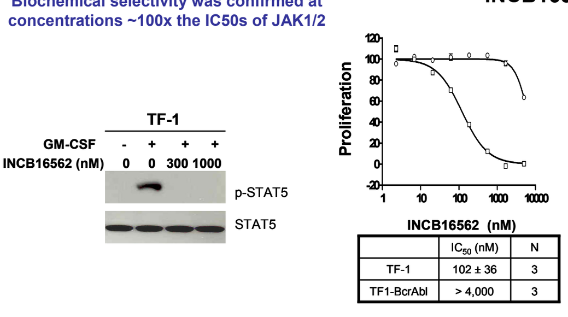
Compound	JAK1	JAK2	JAK3	Tyk2
INCB16562	9	2	1895	32
INCB19408	10	21	1945	94

*performed at 1mM ATP



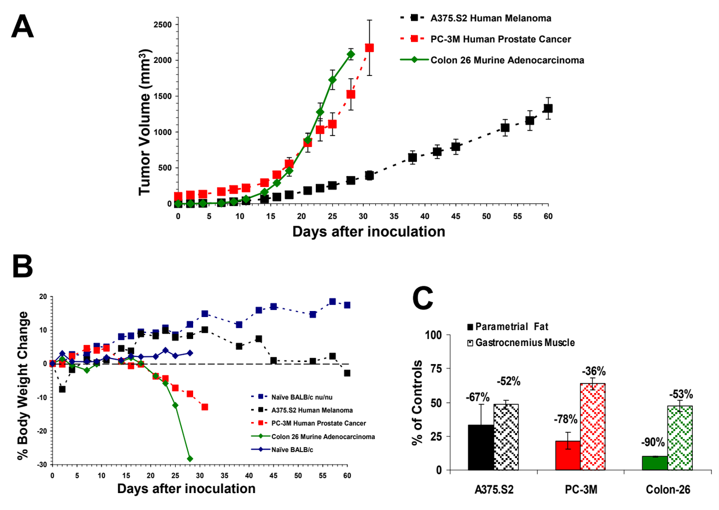
INCB16562

Biochemical selectivity was confirmed at concentrations ~100x the IC50s of JAK1/2

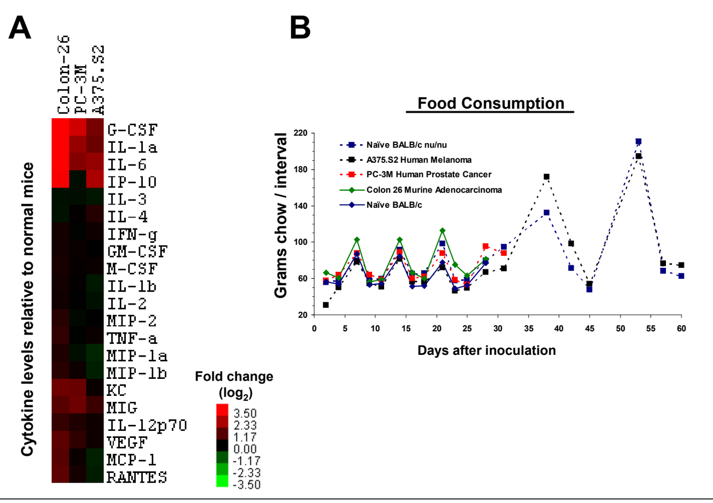


	IC_{50} (nM)	N
TF-1	102 ± 36	3
TF1-BcrAbl	> 4,000	3

2. Tumor growth (A) is associated with loss of total body weight (B), fat and muscle (C)

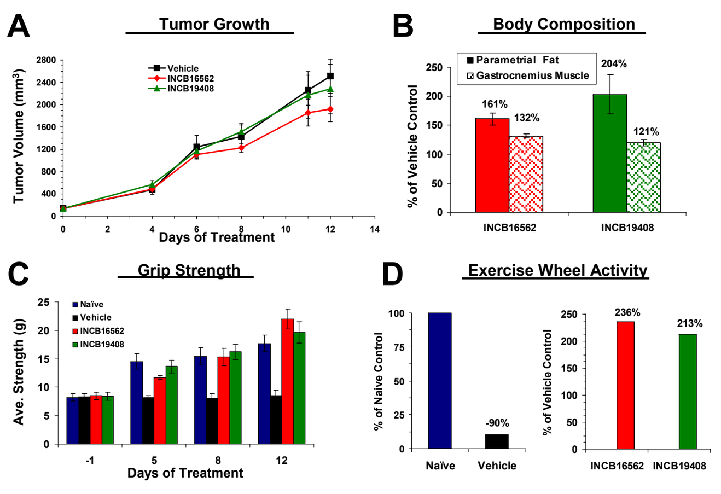


3. Cachectic mice have elevated plasma levels of inflammatory proteins (A) but no changes in food consumption (B)



A
Cytokine levels relative to normal mice
G-CSF
IL-1a
IL-6
IP-10
IL-3
IL-4
IFN-g
GM-CSF
M-CSF
IL-1b
IL-2
MIP-2
TNF-a
MIP-1a
MIP-1b
KC
MIG
IL-12p70
VEGF
MCP-1
RANTES
Fold change (log2)
3.50
2.33
1.17
0.00
-1.17
-2.33
-3.50
B
Food Consumption
Grams chow / interval
Naïve BALB/c
Days after inoculation

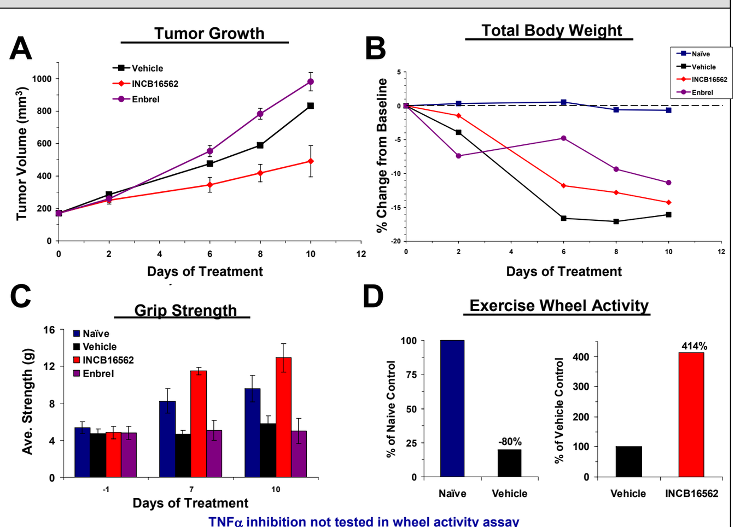
4. JAK1/2 inhibition prevents loss of muscle and fat stores independently of effects on tumor growth resulting in functional improvement in the Colon26 tumor model



A
Tumor Growth
Tumor Volume (mm³)
Vehicle
INCB16562
INCB19408
Days of Treatment
B
Body Composition
Parametrial Fat
Gastrocnemius Muscle
% of Vehicle Control
161%
132%
204%
121%
INCB16562
INCB19408
C
Grip Strength
Ave. Strength (g)
Naïve
Vehicle
INCB16562
INCB19408
Days of Treatment
D
Exercise Wheel Activity
% of Naïve Control
% of Vehicle Control
Naïve
Vehicle
INCB16562
INCB19408

No significant total body weight loss or changes in food consumption during this experiment

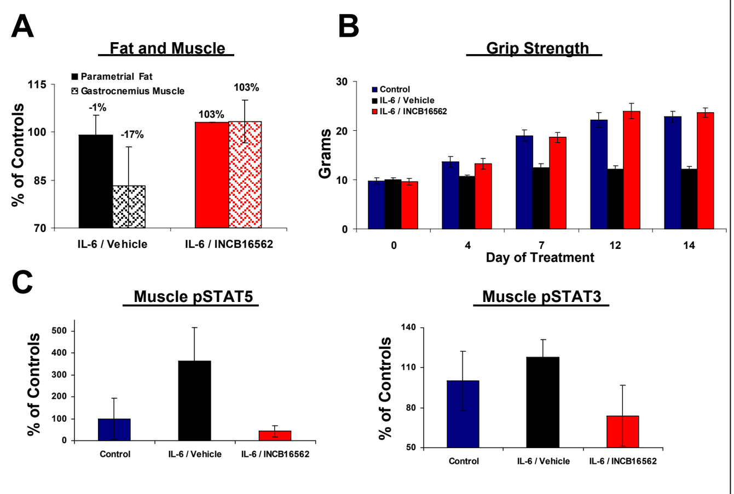
5. In the PC-3M human prostate cancer model, selective JAK inhibition improves cachexia-associated functional endpoints



A
Tumor Growth
Tumor Volume (mm³)
Vehicle
INCB16562
Enbrel
Days of Treatment
B
Total Body Weight
% Change from Baseline
Naïve
Vehicle
INCB16562
Enbrel
Days of Treatment
C
Grip Strength
Ave. Strength (g)
Naïve
Vehicle
INCB16562
Enbrel
Days of Treatment
D
Exercise Wheel Activity
% of Naïve Control
% of Vehicle Control
Naïve
Vehicle
INCB16562

TNFα inhibition not tested in wheel activity assay

6. Infusion of IL-6 causes loss of muscle mass (A) and strength (B) through activation of JAK signaling (C) – reversal by JAK1/2 inhibition



A
Fat and Muscle
Parametrial Fat
Gastrocnemius Muscle
% of Controls
IL-6 / Vehicle
IL-6 / INCB16562
B
Grip Strength
Control
IL-6 / Vehicle
IL-6 / INCB16562
Grams
Day of Treatment
C
Muscle pSTAT5
Muscle pSTAT3
% of Controls
Control
IL-6 / Vehicle
IL-6 / INCB16562

No significant loss of body weight or change in food consumption noted

CONCLUSIONS

- Tumor growth is associated with weight loss and decreased fat and muscle stores without altered food consumption
- Administration of selective JAK1/2 inhibitors improves body composition and physical performance in mouse models of CAC
- High levels of inflammatory proteins were observed in multiple CAC models
- Infusion of IL-6 activates JAK/STAT signaling in skeletal muscle resulting in decreased muscle mass and strength that is prevented by JAK1/2 inhibition
- The selective JAK1/2 inhibitor INCB018424 improves body mass and physical activity in patients suffering from myeloproliferative neoplastic diseases (Verstovsek, ASH 2008)