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PRINCIPAL INVESTIGATOR: Teresa Zimmers, Ph.D.

CONTRACTING ORGANIZATION: University of Miami
Miami, FL 33124

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Teresa Zimmers, Ph.D.

Email: tzimmers@med.miami.edu

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14. ABSTRACT
Epidemiologic evidence demonstrates that caloric restriction and physical activity independently reduce breast cancer potentially by decreasing adiposity and insulin resistance. To determine the role of increased skeletal muscle mass on breast cancer, we sought to measure rates of chemically induced mammary tumorigenesis and progression in genetically hypermuscular mice, including mice lacking the muscle growth inhibitor myostatin and mice expressing a dominant negative form of the myostatin receptor (MLC-dnActRIIB mice). Mammary cancer was induced by a combination of a tumor promoter, medroxyprogesterone acetate, and a carcinogen, dimethylbenz-a-anthracene. Technical difficulties with the model required us to seek a no-cost extension for one year. Further experience indicated that body composition of the mice affected pharmacodynamics of drug administration, i.e. MPA and DMBA given in ethanol and oil had different bioavailability in lean, hypermuscular mice versus mice of normal body type, confounding interpretation of the results. Now we have switched to a genetic model of mammary cancer which we are breeding into our hypermuscular mice and the results are pending. In the interim we used genetic and pharmacological inhibition of the myostatin pathway to potentially preserve muscle in the end-stages of cancer, cancer cachexia. Up to 25% of breast cancer deaths may be attributed to muscle wasting from the complex metabolic syndrome induced by the tumor. However, despite increasing normal muscle growth, myostatin inhibition failed to protect mice from cancer cachexia.

15. SUBJECT TERMS
Breast cancer, skeletal muscle, myostatin, MPA, DMBA, Activin receptor, cachexia.

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A. INTRODUCTION

Epidemiologic evidence demonstrates that caloric restriction and physical activity independently reduce breast cancer. Conversely, obesity and insulin resistance are associated with increased breast cancer incidence, metastasis and mortality. Current data suggest that the heightened glucose and insulin levels of obesity and Type II diabetes synergize with adipose-derived hormones, cytokines and growth factors ("adipokines") to increase mammary cell proliferation and promote tumor angiogenesis. To date no studies have addressed the role of skeletal muscle in breast cancer however, despite the fact that skeletal muscle accounts for 30-50% of energy expenditure, plays a significant role in regulating insulin sensitivity and fatty acid and glucose metabolism, and is a source of cytokines and growth factors, including interleukins, Insulin-like Growth Factor (IGF) isoforms, IGF-binding proteins and myostatin.

To determine the effect of skeletal muscle mass on breast cancer, we sought to measure rates of chemically induced mammary tumorigenesis and progression in genetically hyper-muscular mice. The models we are used were mice bearing targeted deletion of the myostatin gene (Mstn-/- mice) (1) and mice expressing a truncated form of the myostatin receptor, the Activin Receptor Type IIB, specifically in skeletal muscle under control of the myosin light chain promoter (2). The truncated receptor functions as a dominant negative, rendering the muscle resistant to signaling from myostatin and other ActRIIB ligands, including Activin and potentially GDF-11 (2). Both strains of mice exhibit increased skeletal muscle mass and decreased adiposity versus wild-type controls. Reproduction and life span are grossly normal in these mice (unpublished data, T.Z.). Effects of either of these genetic manipulations on mammary tissue have not been characterized. Cows bearing mutations in the myostatin gene, however, are reported to produce less milk, suggesting that myostatin may influence mammary tissue, either directly or indirectly.(3)

In order to induce mammary cancer in these mice, we chose to administer a combination of a tumor promoter, medroxyprogesterone acetate, and a carcinogen, dimethylbenz-a-anthracene, using a published protocol.(4) In the first year, we experienced both high non-tumor associated mortality and low fertility (see below), which required us to seek a no-cost extension of the project. Further study in the second year demonstrated that we were unlike to be able to discriminate differences in tumor latency, size and burden due to the differential bioavailability of the MPA and DMBA during the initial injections, versus effects of improved glucose metabolism and reduced adiposity on tumorigenesis and progression. For this reason, we abandoned the carcinogen model and began mating both lines of hypermuscular mice to a genetic model of mammary cancer, B6.FVB-Tg(C3-1-TAg)cJeg/J mice.(5) These mice, we which had rederived from cryopreserved stocks at Jackson Laboratories, are transgenic for the SV-40 Large tumor antigen (TAg) driven by the rat prostatic steroid binding protein (C3(1))promoter. Female mice transgenic mice develop hyperplasia of the mammary gland ducts and acini by 3 months of age and progress to multifocal mammary adenocarcinoma with death by 6 month of age. Thus initiation in this model is well established, however altered body composition

and metabolism may influence subsequent steps of carcinogenesis, including rate of proliferation and progression. These studies are still in progress.

As those studies progress, we turned to another question relating skeletal muscle and cancer—pathological muscle wasting in cancer cachexia. (6) (7) (8) Cancer cachexia is a devastating complication of breast cancer and other cancer types. Progressive wasting of adipose tissue and skeletal muscle despite adequate food intake results in asthenia, reduced ambulation, diminished quality of life, poor response to therapy, and often death due to respiratory failure or infection. In cancer, cachexia afflicts more than half of all patients and is itself responsible for 25-30% of all cancer-related deaths. Currently, there are no approved treatments for muscle wasting. Previously we showed that administration of exogenous myostatin caused muscle wasting in previously healthy mice. Others have shown that inhibition of myostatin can induce muscle growth and improve the muscle phenotype in mouse models of muscular dystrophy. Thus we sought to determine whether inhibiting myostatin genetically or pharmacologically would preserve muscle mass and improve function in mouse models of cancer cachexia.

B. BODY

The Tasks outlined in our statement of work were:

Task 1. To measure rates and progress of mammary tumorigenesis in genetically lean, hyper-muscular mice. (Months 1-12)

a) Myostatin null mice:
   i) Breed myostatin heterozygous mice to obtain the desired number and genotype: 56 female mstn+/+ and 56 female mstn -/- mice (Months 1-3).
   ii) Treat 40 mice per genotype with the carcinogen, DMBA, once a week for six weeks in the presence of medroxyprogesterone acetate (MPA) (Months 4-5).
   iii) Kill and necropsy mice upon gross evidence of tumor (Months 5-12).
   iv) Perform histopathological analsyis of tumors (Month 12).

b) Muscle-specific dominant-negative Activin Receptor Type IIB transgenic mice:
   i) Breed dnActRIIB+/o mice to obtain the desired number and genotype: 56 female dnActRIIB+/o and 56 female nullizygous mice (Months 1-3).
   ii) Treat 40 mice per genotype with the carcinogen, DMBA, once a week for six weeks in the presence of medroxyprogesterone acetate (MPA) (Months 4-5).
   iii) Kill and necropsy mice upon gross evidence of tumor (Months 5-12).
   iv) Perform histopathological analsyis of tumors (Month 12).

Task 2. To determine levels of hormones, adipokines, and myokines in normal and genetically hyper-muscular mice, with and without mammary carcinogenesis.

a) Serum collection and assay for potential mediators of mammary carcinogenesis, including hormones, adipokines and myokines (specifically estrogen, leptin, adiponectin, insulin, free and bound insulin-like growth factors, insulin-like growth factor binding

proteins, interleukin-6, and growth hormone) in 8 young and 8 aged (1 year) wild-type and hypermuscular mice, for a total of 64 mice. Assays will be performed by a combination of ELISA and multiplex analyte profiling using Luminex technology (Months 3 and 12).

b) Serum collection and assay for potential mediators of mammary carcinogenesis, including hormones, adipokines and myokines (specifically estrogen, leptin, adiponectin, insulin, free and bound insulin-like growth factors, insulin-like growth factor binding proteins, interleukin-6, and growth hormone) in a subset of treated mice at sacrifice upon evidence of mammary tumorigenesis. Assays will be performed by a combination of ELISA and multiplex analyte profiling using Luminex technology (Months 3 through 12).

Task 3. To identify statistical relationships between myostatin genotype and breast cancer-related phenotype.

a) To compare/correlate rates of mammary tumor initiation and progression with myostatin and dnActRIIB genotype (Month 12).

b) To compare/correlate levels of serum hormones, adipokines and myokines with myostatin and dnActRIIB genotype (Month 12).

c) To compare/correlate levels of serum hormones, adipokines and myokines with mammary tumor incidence and stage (Month 12).

d) To compare/correlate levels of serum hormones, adipokines and myokines with mammary tumor incidence and stage and myostatin or dnActRIIB genotype (Month 12).

Final Report

Task 1. To measure rates and progress of mammary tumorigenesis in genetically lean, hyper-muscular mice. (Months 1-12)

Low fertility/high pup mortality resulted in few mice for analysis:

In order to produce the numbers of mice indicated for the study, we set up cages containing triplet matings of one male and two females for each line. Mstn-/- mice have been backcrossed 10 generations onto C57BL6/J, thus rendering them >99% genetically identical to C57BL6/J. Thus we maintained the mstn-/- line by crossing mstn-/- males to mstn-/- females. A line of C57BL6/J mice were similarly bred to serve as controls. The transgenic MLC-dnActRIIB mice are on a mixed genetic background, thus mice hemizygous for the MLC-dnActRIIB transgene were crossed to C57BL6/J mice, with age-matched littermates serving as controls.

Although at least 12 triplet mating cages each were set up for the mstn-/- and MLC-dnActRIIB lines, few pups were born or survived to weaning. Interventions applied to increase fertility included switching the breeders to an enriched diet (“love mash”), providing both cotton and paper nestlets to promote nest building, adding plastic mouse

"igloos" to the cages to provide a nesting environment, and moving the cages to various low-activity, low-vibration regions of the room. We also discovered that the room was routinely experiencing large temperature variations ranging from the low 60s to the high 80s during the day. We suspected that the temperature shifts might be impairing fertility or pup survival, consistent with published reports. Ultimately, working with the Division of Veterinary Resources and Physical Plant, we were able to resolve the temperature fluctuations and maintain the room in the range of 70-75F. This was resolved in mid-March, 2006.

Due to the low fertility rates of the transgenic and knockout lines, most of the female pups generated were put back into the breeding scheme. As a result, we did not attain the numbers of mice required and indicated in the original Statement of Work (40 mice per genotype). We will bred the mice and subjected them to the dosing regimen as described in the Statement of Work during the subsequent one-year no cost extension.

The original model of MPA/DMBA mammary tumorigenesis resulted in high non-tumor related mortality, requiring refinement of the model:

Aldaz et al. described a method using medroxyprogesterone (MPA) to accelerate development and increase incidence of mouse tumors induced by dimethylbenzanthracene (DMBA).(4) They describe implanting 2 subcutaneous pellets (standard release, no binder) of MPA, 20mg each, into 6 wk old female mice. Beginning at nine weeks, DMBA was administered by gavage at a concentration of 1mg/dose in 0.1ml cottonseed oil at 9, 10, 12, and 13 weeks of age. Mice were palpated weekly to identify mammary tumor development.

Using this model, we experienced a nearly 100% mortality rate prior to the end of the DMBA administration, leaving no mice for analysis of mammary tumorigenesis. We ruled out technical issues such as gavage or carrier-associated injury/toxicity as the cause of death. MPA is also known as DepoProvera, a contraceptive in clinical use.

Improved MPA/DMBA model of mammary tumorigenesis:

In humans, DepoProvera is administered as an intramuscular injection every three months. To refine our model and reduce pain and distress, we substituted pellet implantation with subcutaneous injection of MPA, then titrated the DMBA dose in wild-type C57BL6/J mice to identify a dose with minimal toxicity. Ultimately we generated the following treatment scheme:

3 wks – tail cut and genotyping
4 wks – weaning and separation from parents
6 wks – s.c. injection of 20mg MPA
9 wks – gavage with 13.2 mg/kg DMBA in 0.1 ml cottonseed oil
10 wks – gavage with 13.2 mg/kg DMBA in 0.1 ml cottonseed oil
12 wks – gavage with 13.2 mg/kg DMBA in 0.1 ml cottonseed oil
13 wks – gavage with 13.2 mg/kg DMBA in 0.1 ml cottonseed oil

This dosing regimen had markedly increased survival, with 13 of 16 wild-type mice surviving to the end of the treatment schedule.

FINAL OUTCOME: Although we proceeded to put a total of 24 mice of each genotype into the protocol, we became concerned about the possibility that any effects we might observe on mammary carcinogenesis might be due not to the endocrine actions of muscle and adipose tissue, but rather that they may be due to altered drug distribution. There were two points of concern:

1. The possibility that body composition might significantly alter volume of distribution of the drugs and carriers. (The MPA was solubilized in ethanol, while the DMBA is given in cottonseed oil.)
2. Doses of drugs were given according to body weight, while genotoxicity is often thought to scale better to metabolism. Metabolism is a function not only of body size, but also of total body surface area (BSA).

For these reasons, it became necessary to determine body composition as well as BSA in the mice to be used.

Estimating BSA is essential for accurate modeling of drug dosing and toxicity. (9) (10) A century ago Meeh proposed that three-dimensional body volume is proportionate to body mass and so two-dimensional BSA is a functional the two-thirds power of mass: BSA (cm2) = k M(g)$^{0.667}$, where k (Meeh constant) must be empirically determined by species. A Meeh constant of 10 is typically reported for mice. We sought to determine k for different strains of inbred and outbred mice, including mice with genetically altered body composition.

To measure precisely the differences in body composition in the genetically altered mice, we dissected muscles and fat pads from Mstn null mice and wildtype C57BL6/J mice (Table 1). Body composition in dnACTRIIB mice was measured using Piximus imaging, essentially a very low energy, high resolution X-ray imaging system designed for this purpose (Table 2).(11, 12)

To determine BSA, mice were euthanized and weighed; pelts were removed and digitally scanned. BSA was determined using Adobe Photoshop, NIH ImageJ and calibrated standards. Statistical comparisons were made between strains, sexes, and mice of various body compositions using one-way ANOVA with Bonferroni's multiple comparisons test. Fat and lean body mass and percent fat mass were determined by Piximus imaging.

Table 1. Body composition of wild-type and myostatin null mice.

	wild-type	Mstn-/-	N	p
Total Body Mass	22.63 ± 1.140	30.06 ± 0.7127	8	< 0.0001
Quadriceps Mass	0.154 ± 0.0114	0.320 ± 0.0048	8	< 0.0001
Gastrocnemius Mass	0.124 ± 0.0063	0.249 ± 0.0159	8	< 0.0001
Periuterine Fat Mass	0.186 ± 0.0493	0.191 ± 0.0632	8	NS
Liver Mass	1.031 ± 0.0630	1.066 ± 0.0689	8	NS

Calculated BSA using k = 10 was significantly different from the actual BSA for all mice (N = 124, $p < 0.0001$), as well as for mice grouped according to strain or body

composition. These data suggest that the value for *k* in this study was not 10 and was not shared by all mice. Non-linear regression analysis fitting data from all mice to the Meeh equation gave a best-fit *k* of 8.955 ± 0.071 (r^2 = 0.6913). When data from only normal mice were used, a best-fit *k* of 9.662 ± 0.072 was returned with better fit (r^2 = 0.847), indicating that the BSA-mass relationships for mice of altered body composition was different than for normal mice. Indeed, mean *k* values determined from actual BSA and mass across all mice or within subgroups according to strain or body composition were significantly different ($p < 0.0001$, one-way ANOVA) (Table 2). While there was no statistical difference between strains of normal mice, Meeh constants of hypermuscular and obese mice were significantly lower than that of all normal mice as well as their respective background strains (Tukey-Kramer multiple comparisons test). There were no sex differences for *k* across all mice or within any of the strains tested (Student's t-test).

Table 2. Body composition and empirically determined Meeh constant for genetically modified mice.

Strain	Genotype	Pheno-type	N	Total body mass (g)	Meeh constant	Lean body mass (g)	Fat body mass (g)
All			124	18-64	9.12[a]		
C57BL/6J	wt	Normal	22	21-39	9.85[b]	20.72 ± 0.99	4.73 ± 0.30
CD-1	wt	Normal	17	29-53	9.74[c]	26.54 ± 0.89	8.83 ± 0.66
129SVJ	wt	Normal	4	23-30	9.50[d]	ND	ND
SJL/C57	*dnActRIIB*$^{o/o}$	Normal	21	18-35	9.53[e]	24.08 ± 0.67	6.88 ± 0.57
SJL/C57	*dnActRIIb*$^{+/o}$	Hyper-muscular	19	33-43	8.82[f]	33.46 ± 1.18	4.35 ± 0.17
C57BL6/J	*Mstn*$^{-/-}$	Hyper-muscular	20	29-40	8.48[g]	ND	ND
C57BL6/J	*lepr*$^{db/db}$	Obese	21	30-64	8.31[h]	22.00 ± 0.35	29.63 ± 0.38

$p < 0.001$ for b vs a, b vs f, b vs g, b vs h, c vs g, c vs h, d vs h, g vs a, g vs e, h vs e, h vs a; $p < 0.01$ for c vs f; $p < 0.05$ for c vs a, f vs e. ND, not determined.

These results indicate that dosing all of the mice with the same dose of MPA and DMBA per gram body weight would result in an effectively increased dose of the drugs to the hypermuscular mice. Moreover, because MPA and DMBA are lipophilic and will be stored in fat depots, mice with more adipose tissue might be more affected by the same dose.

The uncertainty inherent in the design of the MPA/DMBA study, therefore, renders interpretation of any results exceedingly complicated. For this reason, we chose to abandon the MPA/DMBA study and switched to a genetic model of mammary cancer, B6.FVB-Tg(C3-1-TAg)cJeg/J mice. These mice, we which had re-derived from cryopreserved stocks at Jackson Laboratories, are transgenic for the SV-40 Large tumor antigen (TAg) driven by the rat prostatic steroid binding protein (C3(1))promoter. Female mice transgenic mice develop hyperplasia of the mammary gland ducts and acini by 3 months of age and progress to multifocal mammary adenocarcinoma with death by 6 month of age. Thus initiation in this model is well established, however altered body composition and metabolism may influence subsequent steps of carcinogenesis, including rate of proliferation and progression. We have bred both the Mstn-/- mice and MLC-dnACTRIIB mice into the B6.FVB-Tg(C3-1-TAg)cJeg/J line (Figure 1). These studies

will require several generations of mating to produce mice of the desired genotypes and sex.

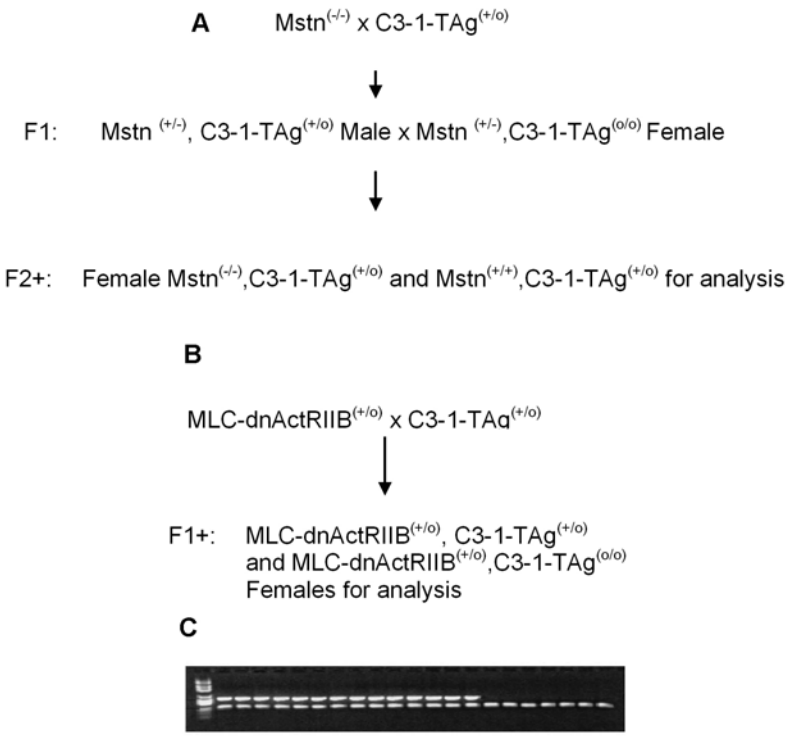

Figure 1 Genetic models of mammary cancer in hypermuscular mice. A and B) Breeding schemes and C) PCR genotyping demonstrating two products in C3-1-TAg transgenic mice, the 474 bp product specific to the C3-1-TAg transgene, and the 200 bp Tcrd internal control (protocol adapted from a JAX protocol), while only the latter is amplified in non-transgenic mice.

Task 2.To determine levels of hormones, adipokines, and myokines in normal and genetically hyper-muscular mice, with and without mammary carcinogenesis.

This task required collecting serum samples from mice of all the indicated strains and genotypes at 8wks and 1 year with no treatment, as well as at sacrifice after MPA/DMBA treatment. We have been collecting the necessary samples as the mice reach the desired age. The samples are being kept at -80C in storage until all of the samples are available. The assays for serum adipokine and myokine levels will be performed once all samples are in hand, thereby minimizing assay variations. We have recently purchased a BioPlex system for multiple analyte profiling in small amounts of serum. This system and commercially available kits will be used.

Task 3. To identify statistical relationships between myostatin genotype and breast cancer-related phenotype.

Obviously this Task requires completion of Tasks 1 and 2, which are still in progress.

Additional Considerations:

In view of the low fertility and precedent for low milk production in myostatin mutant cows, we have determined that a careful analysis of the baseline mammary phenotypes is

required. Therefore, we are collecting mammary glands and making whole mount preparations from virgin, lactating, involuting and aged mice, particulary of the Mstn-/- and wild-type strains. These will be analyzed as part of this project.

New Task 4: Determine the effects of manipulating myostatin signaling to preserve muscle mass in cancer cachexia.

Because the genetic model will require a much longer time to accomplish and necessitates a long wait prior to analysis of the tumor phenotype, we also sought to answer a related question in cancer biology, namely, what is the effect of the myostatin pathway on muscle wasting in cancer cachexia.

Cachexia, or progressive loss of adipose tissue and skeletal muscle not due to starvation, is a feature in many chronic diseases such as cancer, sepsis, burns, AIDS, and organ failure. Myostatin inhibits muscle hypertrophy and hyperplasia. Mice, dogs and humans genetically deficient in myostatin show a 2-5 fold increase in skeletal muscle mass. Conversely, we have shown that myostatin over-expression causes cachexia. Myostatin activity can be inhibited by a binding protein, Follistatin, which can be induced with the antifungal, antibiotic Trichostatin A (TSA), a histone deacetylase inhibitor. TSA has been shown to reduce muscle degeneration in a mouse model of muscular dystrophy. We sought to determine the extent to which inhibiting myostatin activity pharmacologically or genetically might promote muscle preservation in cancer cachexia.

In the genetic model, C57BL6/J myostatin null mice and age (~12 wks) and sex-matched wild-type controls were injected with B16.F10 melanoma cells, a well-characterized model of cancer cachexia. Mice were weighed and tumors measured daily. Mice were humanely euthanized 17-21d after injection.

Tumor size, fractional weight loss, and fractional muscle mass were not different in myostatin null mice versus wild-type mice (Student's t-test). However, there was a trend towards greater fractional fat loss (35% ± 20.2 vs. 20.35% ± 19.45%, n = 12 per group, $p = 0.0844$), along with increased markers of inflammation, including greater total spleen mass ($p = 0.01$) and greater liver to body mass ratios ($p < 0.0001$) at lower fractional tumor burdens in myostatin null mice. **This result indicates that myostatin null mice are not protected from cancer cachexia and moreover, may actually be more sensitive to tumor-induced inflammation.**

In the pharmacological model, CD2F1 mice were injected with colon-26 (C26) adenocarcinoma cells. Once tumors were visible (at 9 days after injection), TSA was administered by daily i.p. injection (0.6 mg/kg body weight in DMSO) for 7d prior to euthanasia. Control C26 mice received DMSO only. Non-tumor bearing mice received either TSA or DMSO on the same schedule as tumor bearing mice. Follistatin and myostatin mRNA levels were assayed by quantitative real-time RT-PCR.

In the pharmacological model, TSA treatment induced follistatin expression 2.5 fold in non-tumor bearing mice and 1.5 fold in C26 mice. Moreover, TSA reduced myostatin

expression 50% in non-tumor bearing mice and 20% in C26 mice. Consistent with reduced myostatin activity, the gastrocnemius from TSA only mice were 22% larger than DMSO only controls ($p < 0.001$). TSA treatment did not protect mice from C26 wasting, however. Percent body weight loss, fat loss and skeletal muscle loss were statistically indistinguishable in TSA versus DMSO treated C26 mice.

Thus, neither genetic nor pharmacological inhibition of myostatin activity was sufficient to prevent or reduce muscle wasting in two models of cancer cachexia. These results suggest that despite their promise in muscle dystrophies, myostatin inhibitors may not be effective in diseases associated with chronic inflammation.

C. KEY RESEARCH ACCOMPLISHMENTS

- □ Gained expertise in whole mount mammary gland preparations and histology.
- □ Resolved environmental control issues relating to low fertility to increase numbers of mice available for study.
- □ Established in our hands and refined the MPA/DMBA model to reduce non-tumor related toxicity.
- □ Determined that dosing should be made relative to body surface area and not to total body weight.
- □ Determined that the relationship of body surface area and body mass in hypermuscular mice is significantly different from that in mice of normal body composition (calculated Meeh constants for our lines).
- □ Measured body composition in our normal and hypermuscular lines of mice.
- □ Determined that the MPA/DMBA model as used might reflect differences in genotoxicity due to body composition and drug distribution, complicating evaluation of our hypotheses.
- □ Rejected the MPA/DMBA model in favor of the genetic model.
- □ Re-derived the B6.FVB-Tg(C3-1-TAg)cJeg/J model of mammary cancer.
- □ Mated our hypermuscular lines into the B6.FVB-Tg(C3-1-TAg)cJeg/J line.
- □ Banked blood and tissue specimens from genetically modified mice and controls, but only those without tumors.
- □ Determined that genetic ablation of myostatin does not ameliorate muscle wasting in a model of cancer cachexia.
- □ Determined that induction of the myostatin inhibitor, Follistatin, by Trichostatin A does not ameliorate wasting in a model of cancer cachexia.
- □ Identified a trend towards increased sensitivity to tumor-related inflammation and cachexia in myostatin null mice.

D. REPORTABLE OUTCOMES

Abstracts submitted to the Association of American Surgery and International Cachexia meetings:

Cheung MC, Gutierrez JC, Spalding PB, Balkan W, Namias N, Koniaris LG, Zimmers TA. (2007)Body Surface Area Prediction in Normal, Hypermuscular and Obese Mice. Association for Academice Surgery Abstract 08-AB-536-ASC.

Link M, Aydogdu T, Guo S, Konairis LG, Zimmers TA. (2007) Genetic and Pharmacologic Inhibition of Myostatin for Muscle Preservation in Cancer Cachexia. Association for Academic Surgery Abstract 08-AB-513-ASC.

E. CONCLUSIONS

Due to complications relating to drug distribution and dosing, we have tried and rejected the MPA/DMBA model of mammary tumorigenesis in favor of a genetic model. We will ultimately determine whether hyper-muscularity and low adiposity confers a protective effect against mammary tumor incidence and progression. As well, we will describe the profile of serum adipokines and myokines in these models and their wild-type counterparts. We have determined definitively that neither genetic nor pharmacological inhibition of myostatin activity was sufficient to prevent or reduce muscle wasting in two models of cancer cachexia. These latter results suggest that despite their promise in muscle dystrophies, myostatin inhibitors may not be effective in diseases associated with chronic inflammation.

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G. APPENDICES

None.