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1–01

Regeneration of the rat tibialis anterior muscle is impaired despite induction of the SPARC-beta-catenin pathway during post-immobilization recovery

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Background and aims: The immobilization-induced tibialis anterior (TA) muscle atrophy worsens after cast removal concomitantly with changes in the extracellular matrix composition. SPARC is a matricellular glycoprotein involved in tissue response to injury and in stabilization of *f*nbeta-catenin, which induces muscle regulatory factors (MRFs) controlling muscle regeneration. We hypothesized that SPARC expression changed upon immobilization and could be involved in the worsening of TA muscle atrophy by altering muscle regeneration processes pending cast removal.

Methods: Wistar rats were subjected to hindlimb immobilization for 8 days (I8) or not (I0), and allowed to recover for 1 to 10 days (R1-10). Expression of SPARC, beta-catenin, and proliferative (i.e. MyoD and MyF5) or differentiation (i.e. myogenin) MRFs were assessed by Western blots and/or RT-qPCR during recovery of previously immobilized TA.

Results: SPARC mRNA levels increased only during recovery at R1 (+161 %) and R10 (+200 %), compared to I8 and I0. beta-catenin mRNA levels increased at I8 (+80 %) and R10 (+190 %), while protein levels accumulated from R1 to R10 (+350 to 400 %) in immobilized TA vs. I0. MyoD and MyF5 mRNA levels increased by 2–3 fold only at I8 and R1 in immobilized TA vs. I0. By contrast, myogenin mRNA levels decreased at I8 (−60 %) and R1 (−90 %), and increased at R10 (+100 %).

Conclusions: We report an induction of the SPARC-beta-catenin pathway associated with increased mRNAs of the proliferative MRFs (Myf5 and MyoD) in the recovering TA early after cast removal. The differentiation MRF myogenin was first largely repressed, but increased later on, when TA started to recover. Altogether, the data suggest that the TA tended to preserve muscle regeneration potential through induction of proliferative MRFs. However this process was poorly efficient presumably because of an alteration in satellite cell differentiation.

1–02

Upregulation of genes involved in muscle protein breakdown coincides with downregulation of genes involved in the immunoproteasome in a cancer cachectic C26 mouse model

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Background: Cachexia is characterized by loss of muscle mass and is associated with complications like a reduced immune response. In cancer patients with low level of immunoproteasome expression, tumour-and infection-derived epitopes have been suggested to have a higher chance of escaping from immune surveillance. Here we present the C26 adenocarcinoma mouse model derived data on transcriptomics analysis of two highly interconnected systems: the muscle protein breakdown, ubiquitin-proteasome and the immunoproteasome pathways.

Methods: Male CD2F1 mice, aged 5–6 weeks, were randomly divided into a control (C) or a tumour-bearing group

being evaluated in two Phase III trials enrolling patients with non-small cell lung cancer (NSCLC) and cachexia.
Methods: HT-ANAM-301 (NCT01387269) and HT-ANAM-302 (NCT01387282), also known as ROMANA 1 and ROMANA 2, are double-blind, placebo-controlled, randomized (2:1 anamorelin HCl vs. placebo) Phase III trials in patients with NSCLC cachexia (target of 477 patients per study). Patients receive once daily anamorelin HCl (100 mg) or placebo for 12 weeks. Eligible patients must have unresectable Stage III/IV NSCLC and cachexia (body weight loss >5 % within prior 6 months or BMI <20 kg/m2). Co-primary endpoints are change from baseline in LBM as measured by DXA scan and in muscle strength as measured by handgrip strength. Secondary endpoints include change in body weight, overall survival, and quality of life. Population pharmacokinetics is included in HT-ANAM-301. After 12 weeks of treatment, patients may continue in a separate 12-week safety extension study (HT-ANAM-303 [ROMANA 3] NCT01395914).
Results: Enrollment in ROMANA 2 completed in June 2013. Of the 495 randomized patients, preliminary data indicate that at baseline, 71 % had Stage IV cancer and 67 % were ECOG 1 performance status. All key baseline characteristics will be presented for ROMANA 2.
Conclusions: Anamorelin HCl is undergoing Phase III evaluation, where one trial has completed enrollment and the other is nearing completion. Efficacy and safety results are awaited.

5–03
Individually dose-optimized Phase I-II study with natural ghrelin in advanced cancer patients with cachexia

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Background: Natural ghrelin, a peptide growth hormone secretagogue has a therapeutic potential in cachexia. We designed a dose-finding trial of subcutaneous natural ghrelin to improve nutritional Intake (NI) in advanded cancer patients.
Methods: Advanced cancer patients with cachexia management (symptom management, physiotherapy, nutritional and psychosocial support) started with ghrelin at 32 μg/kg, followed by 50 % dose increases. Patients self-injected ghrelin twice daily for 4 days followed by a wash-out period. Pharmacokinetics was measured. After reaching the primary endpoint: Minimal Dose for Maximal Nutritional Intake(MD-MANI) defined as ≥10% NI increase [2 days food diaries, weighing food at home] reaching a plateau or maximum tolerated dose (MTD), a maintenance period followed, where patients injected 10 doses of ghrelin per week. Safety parameters, NI, and cachexia outcomes (symptoms, narratives, muscle mass and strength) were measured over 6 weeks.
Results: 10 patients with metastatic solid tumors were included and 6 received ghrelin. Median survival was 59 days (28–412 days). 5 patients reached the primary endpoint and 3 patients reached the end-of study visit. MD-MANI was reached on dose level 3 (72 μg/kg) in 3 patients, dose level 2 & 4 in 1 patient each. Final pharmacokinetic results are pending. On request, two patients were approved to receive ghrelin on compassionate use. Subjective tolerability was high. An episode of hypothermia occurred as related, one atrial fibrillation and a secondary malignancy as unrelated adverse events. Of the 6 patients reaching MD-MANI muscle mass was stable in 2 patients, increased in 1 patient, muscle strength was stable in 3 patients. Selected narratives were: "I feel fresher and I eat more", "This is the first therapy which improves my well-being".
Conclusion: Ghrelin was safe in patients with cancer cachexia without dose-limiting toxicity and well tolerated. There was a positive effect on nutritional intake and patient narratives.

5–04
Phase II study of OHR/AVR118 in anorexia-cachexia

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OHR/AVR118, a peptide drug to manage symptoms of anorexia-cachexia modulates cytokine action. The study objectives were to determine the effect of OHR/AVR118 on appetite, early satiety and nutritional intake in patients with advanced cancer. Secondary endpoints included changes in performance status, lean muscle mass and quality of Life (QOL). Eligible adult patients received 4.0 ml of OHR/AVR118 subcutaneous daily injections. Patients underwent bi-monthly evaluations during the 28 day initial treatment (phase A). Evaluations included Karnofsky performance status, Edmonton Symptoms Assessment Scale (ESAS), Patient Generated Subjective Global Assessment (PG-SGA), Simmonds Functional Assessment, Dyspepsia Symptom Severity Index, Weight, Lean Body Mass, skin fold thickness and grip strength.

Eighteen patients, 3 with stage III and 15 with stage IV cancers completed the treatment protocol; six pancreatic cancer, five lung cancer, two prostate cancer patients, and one each with colon, stomach, esophageal, liver cancer and multiple myeloma. At completion of treatment, patients achieved stabilization of mean body weight, body fat and muscle mass with a significant increase in appetite ($p = .001$). Moreover, PG-SGA (Patient Generated Subjective Global Assessment) scores demonstrated improvement ($p = .025$), indicating improved nutritional status. No statistically significant differences from baseline (indicated by the paired t test) were observed in body fat content, arm circumference, triceps fold measurement, nausea or vomiting.
Patients had the option to continue receiving study drug after the initial 28 day treatment period; 11 of 18 patients (61 %) elected to do so, being treated with the drug for a total of 42 to 153 days. Sustained body weight stabilization was maintained on prolonged therapy with the drug in this sub-group of patients. These results were seen despite the fact that 7 of the 18 patients received concomitant chemotherapy, and 1 received radiotherapy during the trial treatment period with OHR/AVR118. The drug was well tolerated by the patients in the study.

5–05
Siltuximab reverses muscle wasting in patients with multicentric Castleman's disease

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Background and Aims: Multicentric Castleman's disease (MCD) is characterized by fevers, night sweats, fatigue, anorexia, and wasting. IL-6 plays pivotal roles in MCD and muscle wasting. Siltuximab (siltux), a chimeric IgG1κ Mab binds IL-6. We studied prospectively collected CT scans to assess siltux's effects on muscle mass (MM).
Methods: Patients (Pts) ($n = 37$) were treated with siltux in a phase I study q wk, 2 week or 3 week at doses from 2.8 to 11 mg/kg, and 34/37 pts had CTs suitable for analysis. Median age was 49 (range 18–76) with 18 M/16 F. Median pt wt was 78 kg (range 40–170). CTs were landmarked at the L3 vertebra. L3 images were analyzed using Slice-O-Matic® with Hounsfield units set at different levels for each tissue.
Results: During siltux txt 38 % of pts gained >1 kg of MM, 2.3±1.1 (mean ± SD or range), 47 % of pts had stable MM ± 1 kg, 0.2±0.5 and 15 % of pts lost >1 kg, loss 3.1±1.7. For all pts ($n = 34$) MM gain was 0.5 kg (−5.5 to.4.4); and fat mass (FM) gain was 3.1 kg (−13.8 to 35.8). By Cheson criteria MM change was 0.9 kg in PR pts ($n = 11$), 0.5 kg in SD pts ($n = 22$), and −3.7 kg in a PD pt. FM change was 8.5 kg for PR pts, 2.85 for SD pts and −0.6 for a PD pt. At phase II dose 11 mg/kg q 3 week ($n = 17$), gain in MM was 0.6 kg (−5.5 to 4.4). Interestingly FM increased first followed by a delay and then MM gains occurred. Pts responding to siltux gained MM up to time of censoring.
Conclusions: In addition to durable MCD objective responses (median response duration not reached at 29 mths follow-up), siltux reversed MM wasting in 38 % of pts, stabilized MM in 47 % and in only 15 % did MM decrease.

5–06
Food aversion and ingestion in patients with breast cancer undergoing systemic chemotherapy

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Background: Cancer patients frequently develop food aversion -even before receiving systemic chemotherapy (SC)- a treatment know to further increase it. A decreased food ingestion ensues food aversion, and adds up to the toxic effect of SC on the digestive tract (mucositis, nausea, vomit and/or diarrhea).
Aim: To describe the most common food aversions on patients with infiltrative breast cáncer (IBC) and to compare food ingestion before and 12 days after the infusion of SC.
Methods: Food ingestion was assessed in 30 patients before and 12 days after receiving the first cycle of SC (anthracyclines and/or taxanes). A questionnaire including seven items aimed to assess the number and type of food aversions was administered. Categoric variables were expressed as frequencies and proportions, and continuous variables were referred using measures of central tendency and dispersion. In order to calculate the differences in ingestion, the Student's t test for related samples was used.