

RAC Protocol 890

GHRH Plasmid Therapy for Cancer

Cachexia

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Cancer Cachexia

The word originates from Greek words “Kakos” and “Hexis” meaning “Bad condition”

Occurs in 80% of advanced cancer and accounts for 20% of deaths

Reduces performance status, quality of life and ability to tolerate or respond to chemotherapy

Starvation and cachexia are not synonymous

Tisdale MJ, Nat Rev Cancer 2002

Slaviero KA, Nutr Cancer 2003

Cancer Cachexia

- Over 5% weight loss over a 12 month period
- ~ 5 million persons affected in the U.S.
- Cachexia complicates the clinical course of COPD, CHF, AIDS, CRF, Cirrhosis, RA, IBD, cystic fibrosis, thyrotoxicosis, Type 1 DM

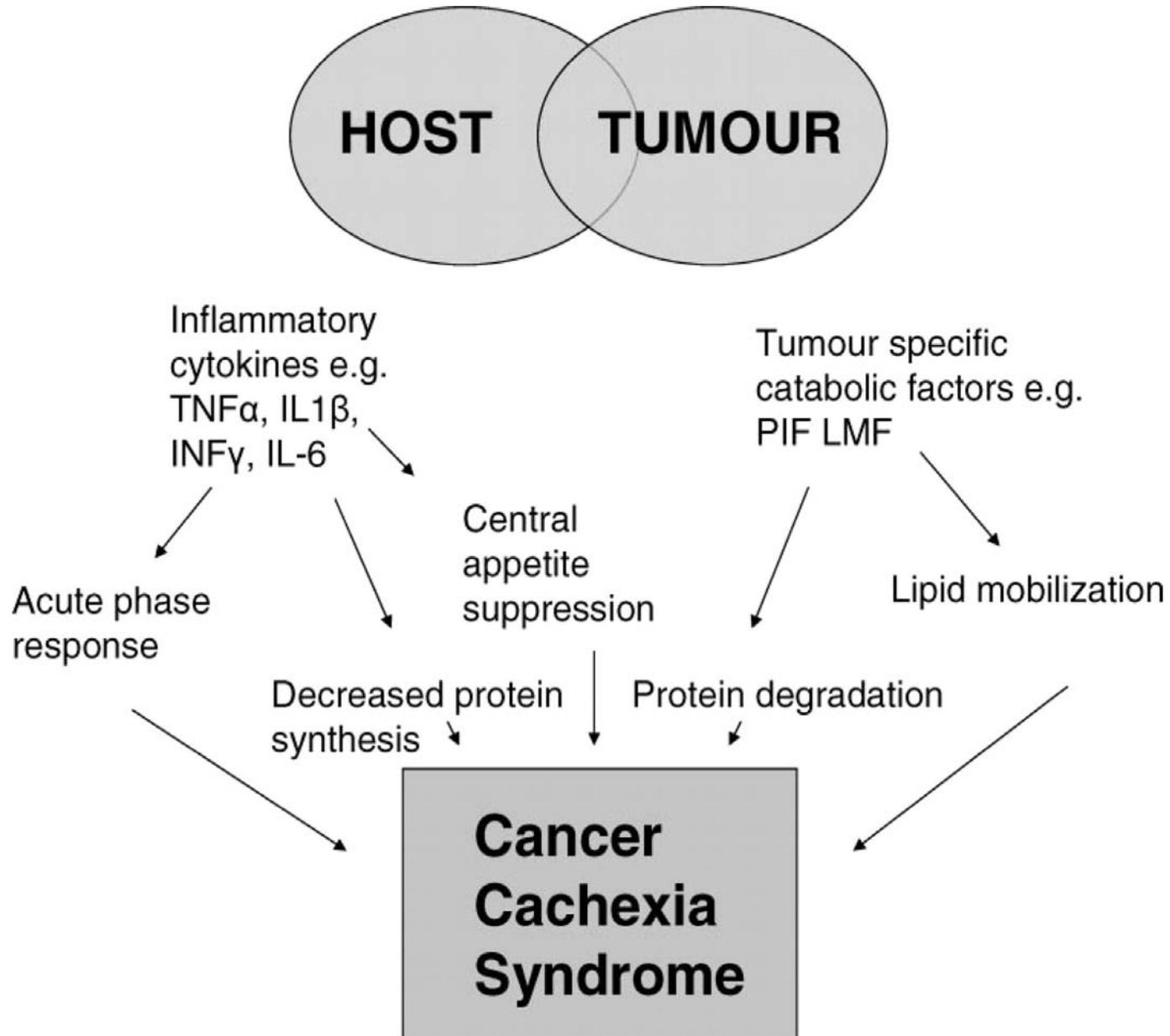
Starvation versus Cachexia

	Starvation	Cachexia
Appetite	Increased	Decreased
Resting energy expenditure	Decreased	Increased
Acute phase response	No	Yes
Skeletal muscle	Maintained	Decreased
Adipose tissue	Decreased	Decreased
Liver size	Decreased	Increased

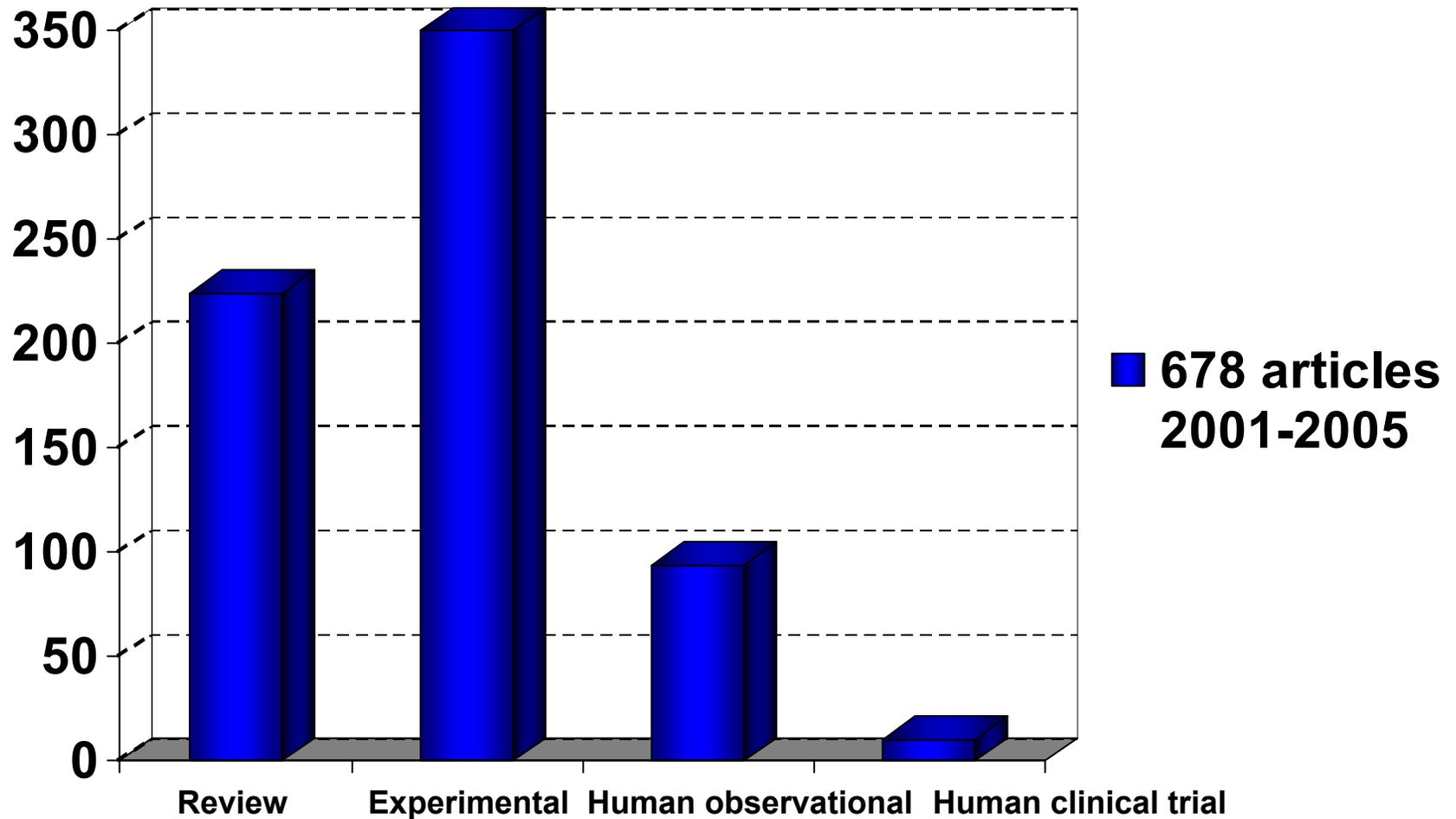
Clinical Characteristics of Cachexia

- Cachexia ↓ quality and quantity of life
- Increased levels of TNF- α , IL-6, plasma angiotensin II, norepinephrine and aldosterone
- Results in insulin resistance, lipolysis and anorexia
- 20-30% of patients with cachexia are anemic

Mechanism of Cancer Cachexia



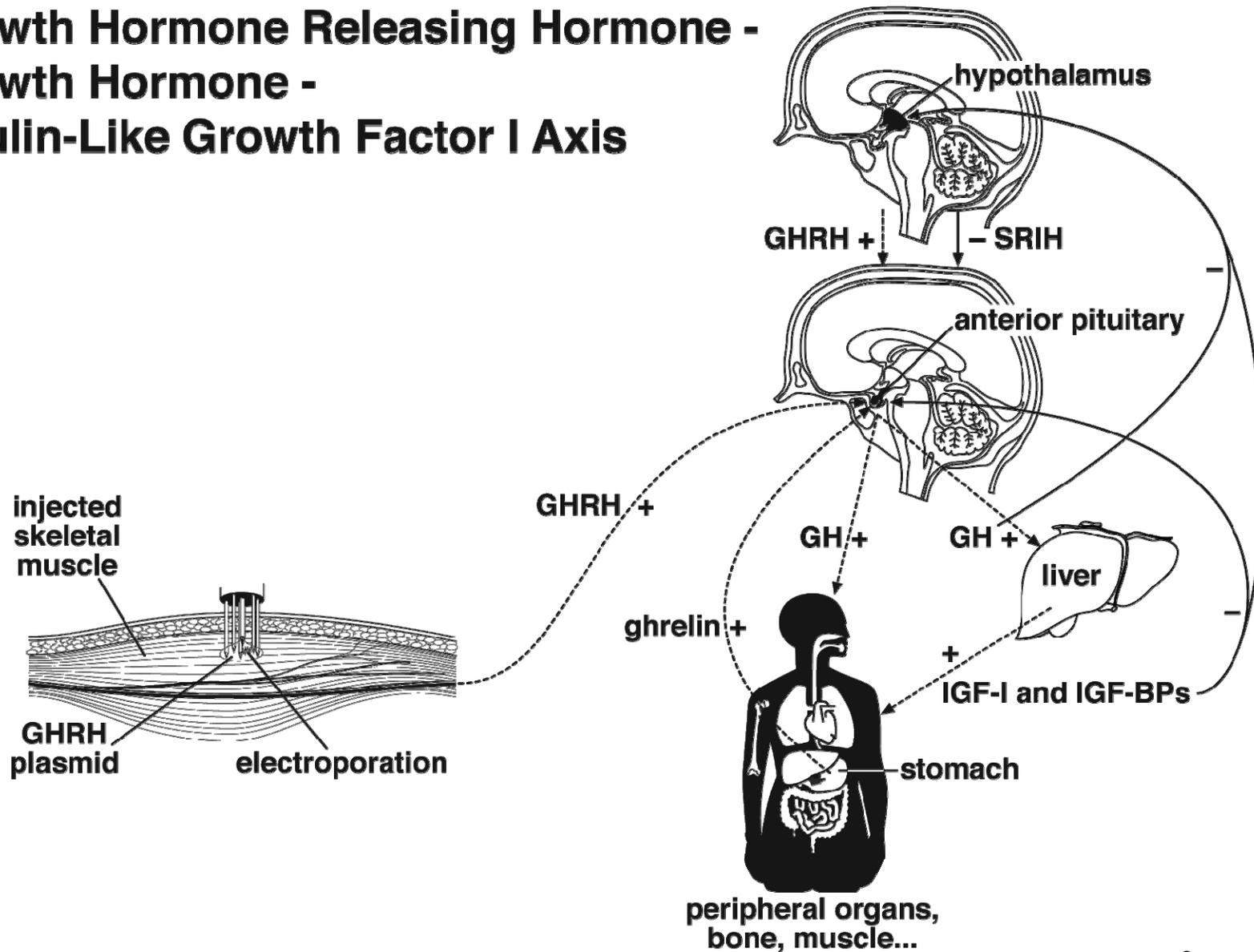
Scientific articles on cancer cachexia



Therapies for Cachexia

- Megesterol acetate (progesterone analogue) approved for therapy
- Medical marijuana approved for appetite stimulation in AIDS patients with cachexia
- Gherlin (hormone secreted in stomach—promotes secretion of GH), oxandrolone (testosterone analogue), ACE inhibitors in Phase II/III trials to support claims for treatment of cachexia

Growth Hormone Releasing Hormone - Growth Hormone - Insulin-Like Growth Factor I Axis



Targeted Patient Population for GHRH plasmid + EP trial

- Patients with diagnosis of advanced cancer with life expectancy of > 3 months and cachexia. ECOG performance status of < 3 who can give informed consent will be enrolled.
- Patients have exhausted most available therapeutic options and have incurable malignancy.

GHRH plasmid mediated therapy

GHRH, GH, IGF-I

Available Therapies = Recombinant Proteins

Short half-life in serum

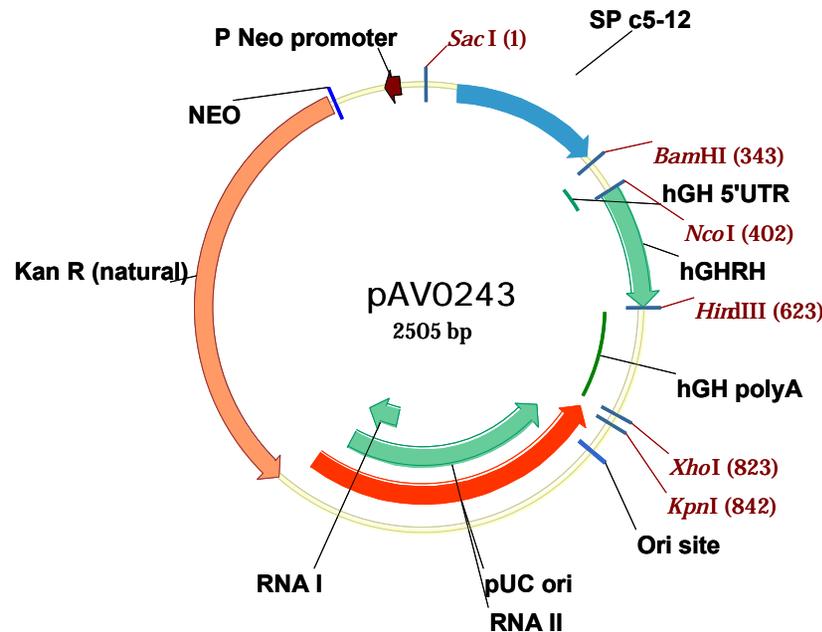
Frequent administration necessary (s.c., i.v.)

Lack of proven orally bio-available formulations

Adverse effects due to supra-physiological levels

Low compliance of patients

Solution: Plasmid Mediated Therapy

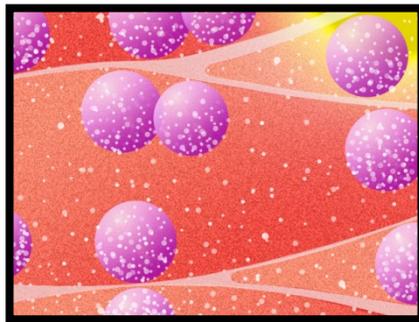


GHRH-expressing plasmid VGX-3200

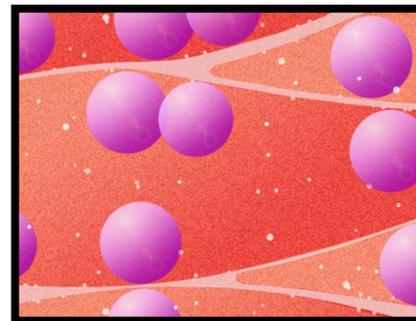
- **Plasmid backbone:**
 - Synthetically produced
 - CpG depleted
 - No known elements that promote integration
 - Only elements needed for plasmid replication and selection
- **Expression cassette:**
 - Muscle specific promoter (expresses only in muscle cells)
 - Human GHRH (1-40)OH cDNA

Why use electroporation for DNA delivery?

- Favard *et al.*, Electrotransfer as a non viral method of gene delivery. *Curr Gene Therapy* 2007 Feb;7(1):67-77.
- Babiuk *et al.*, Delivery of DNA vaccines using electroporation. *Methods Mol Med.* 2006;127:73-82.
- Heller & Heller, *In vivo* electroporation for gene therapy. *Human Gene Therapy* 2006 Sep;17(9):890-7.
- Prud'homme *et al.*, Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases. *Curr Gene Therapy* 2006 Apr;6(2):243-73.



**Plasmid uptake
with
electroporation**

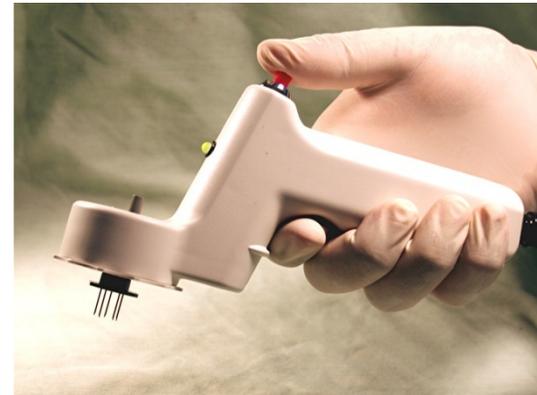


**Plasmid uptake
without
electroporation**

CELLECTRA™ Adaptive Constant-Current Electroporation System



IM applicator



CAUTION Investigational device. Limited by Federal (or United States) law to investigational use.
CELLECTRA™ ADAPTIVE CONSTANT CURRENT ELECTROPORATION DEVICE (Version 1.2) - Quick-Start Instruction

Preparation and Assembly

1. Unpack and fill reusable lid.
2. Remove power switch on the right side of unit if off.
3. Attach applicator to the applicator connector.
4. Turn unit on (Display mode: VOX Pharmaceuticals CELLECTRA Version 1.2, Date/Time).

Activation

1. Unit now powered "ON" (If not powered correctly, simply restart it).
2. Current operating parameters appear and should read:

Preparation: 0.5 sec
 Pulse Delay: 40
 Frequency: 1000 Hz

Before Charging
 Plug charger into the wall outlet and use the Cellectra's cap with the cord to the "OFF" position. The unit is fully charged when a small light inside the cap is illuminated. The unit is fully charged when the unit is still charging. If the cord is in the "ON" position, the battery will not charge.

Directions for Use

1. Prepare the suspension site - using an anti-oxidant soap or equivalent, ensure skin surface is dry before proceeding.
2. Press activation button on applicator and enter the sequence number, i.e. the sequence option (0). Once pressed (0) light on applicator will turn green.
3. Place a disposable electrode strip in the receptacle of the applicator. Turn circular mechanism counterclockwise to lock (if possible).
4. Insert needle and all electrodes firmly into muscle (avoid all surface blood vessels).
5. Conduct impedance check by pressing initiation button on applicator.
 - a) If a RED light and audible alarm sounds, (1) remove applicator and apply (2) press any button to clear display screen (3) re-insert with a different site (4) repeat impedance check from Step 4 above by pressing initiation button on applicator.
 - b) Repeat step (a) above until a GREEN light appears.
6. When impedance test is successful and a GREEN light appears, insert syringe into the center hole of the applicator and pull up on the syringe to ensure the needle is not in a blood vessel.
7. Before the syringe contains muscle, After injection, remove syringe and dispose of in Sharps Disposal Container.
8. Remove firm grip on muscle and applicator. Immediately, press initiation button on applicator to start the 4 second count down timer for firing, as audible alarm may sound.
9. Hold applicator firmly, electro-poration may cause muscle contractions.
10. If any current amount of current was delivered, the original operating parameters will appear on the display screen.
 - If less than 87% of the desired current was delivered, the amount of current will be displayed with the lowest limit and average of delivered current. If 85-90% of the desired current was delivered, the display will read "possible electro-poration error". If error is displayed, turn the applicator OFF.
11. Upon completion, wait 2 to 3 seconds after electro-poration before gently removing strip from muscle. Turn circular mechanism clockwise and carefully remove strip and dispose of in Sharps Disposal Container. Dispose of the applicator in Biohazard Waste Container.

11/07/2007
 P/N: 40009 D01

Protocol Summary

- **Primary Objective:**
- To evaluate the safety and tolerability of escalating doses (0.35 mg, 1 mg, and 3.5 mg) of VGX-3200 (plasmid DNA expressing human growth hormone releasing hormone (hGHRH)), administered intramuscularly in combination with electroporation (EP) to patients with cachexia due to cancer and cancer treatment (Patients will be followed for one year after dosing)

Protocol Summary (cont'd)

Secondary Objectives:

- To estimate the clearance rate and maximum concentration of hGHRH achieved by this treatment.
- To describe the effects of VGX-3200 on: weight; lean and fat body mass; hematological parameters; fasting serum chemistry; lipid profiles and appetite.
- To determine whether the rise of serum hGHRH level is proportional to the amount of plasmid electroporated.
- To estimate the dose of VGX-3200 required to achieve blood levels of insulin-like growth factor – one (IGF-I) to 1.25 x baseline.
- To assess the tolerability by Visual Analog Scale (VAS) of electrical impulse delivery administered intramuscularly with CELLECTRA™ electroporation device.

Inclusion Criteria

- Written informed consent in accordance with institutional guidelines;
- Diagnosis of advanced (metastatic) cancer and/or in remission following treatment;
- Males and females, at least 21 years of age;
- Women of child-bearing potential (WOCBP) must remain sexually abstinent, use medically effective contraception (oral contraception, barrier methods, spermicide, etc), or have a partner who is sterile (i.e., vasectomy) for **1 year after dosing**;
- Performance Status: ECOG score <3;
- Must be ambulatory and able to lay still for at least 30 minutes;
- **Documented weight loss of at least 5% within the last 12 months**;
- Life Expectancy of at least 3 months.
- Patients taking any precautionary concomitant medications specified in the protocol must be on stable doses for >4 weeks prior to enrollment and have no plans to change medications or doses for the duration of the study.

Exclusion Criteria

- Body mass index (BMI) ≥ 30 ;
- **Diabetes requiring insulin or an oral hypoglycemic agent;**
- Chronic infection with hepatitis B or C viruses;
- **Treatment with megestrol or testosterone;**
- **Cytotoxic or radiation treatment within 28 days of study drug administration;**
- Transaminases $> 3 \times$ ULN; Total bilirubin > 3.0 mg/dL; Creatinine > 2.0 mg/dL; Platelets $< 75,000/\text{mm}^3$; absolute neutrophil count $< 1,000/\text{mm}^3$
- Uncontrolled or significant cardiovascular disease including myocardial infarction within 6 months, uncontrolled atrial arrhythmia, uncontrolled hypertension, Class III-IV New York Heart Association (NYHA) congestive heart failure or clinically significant ventricular arrhythmias;
- **Patient is currently participating or has participated in a study with an investigational compound or device within 30 days of signing informed consent;**
- Concurrent anticoagulation or antiplatelet treatments (except for low-dose, 81 mg daily aspirin);
- Metal implants at the site of injection;
- Pregnant or breast feeding subjects or expecting to conceive within 1 year following study treatment.

Issues to Discuss

- Data on GHRH secretion from skeletal muscle
- GHRH effects on tumor growth
- Plasmid persistence
- Informed consent

GHRH secretion from muscle cells

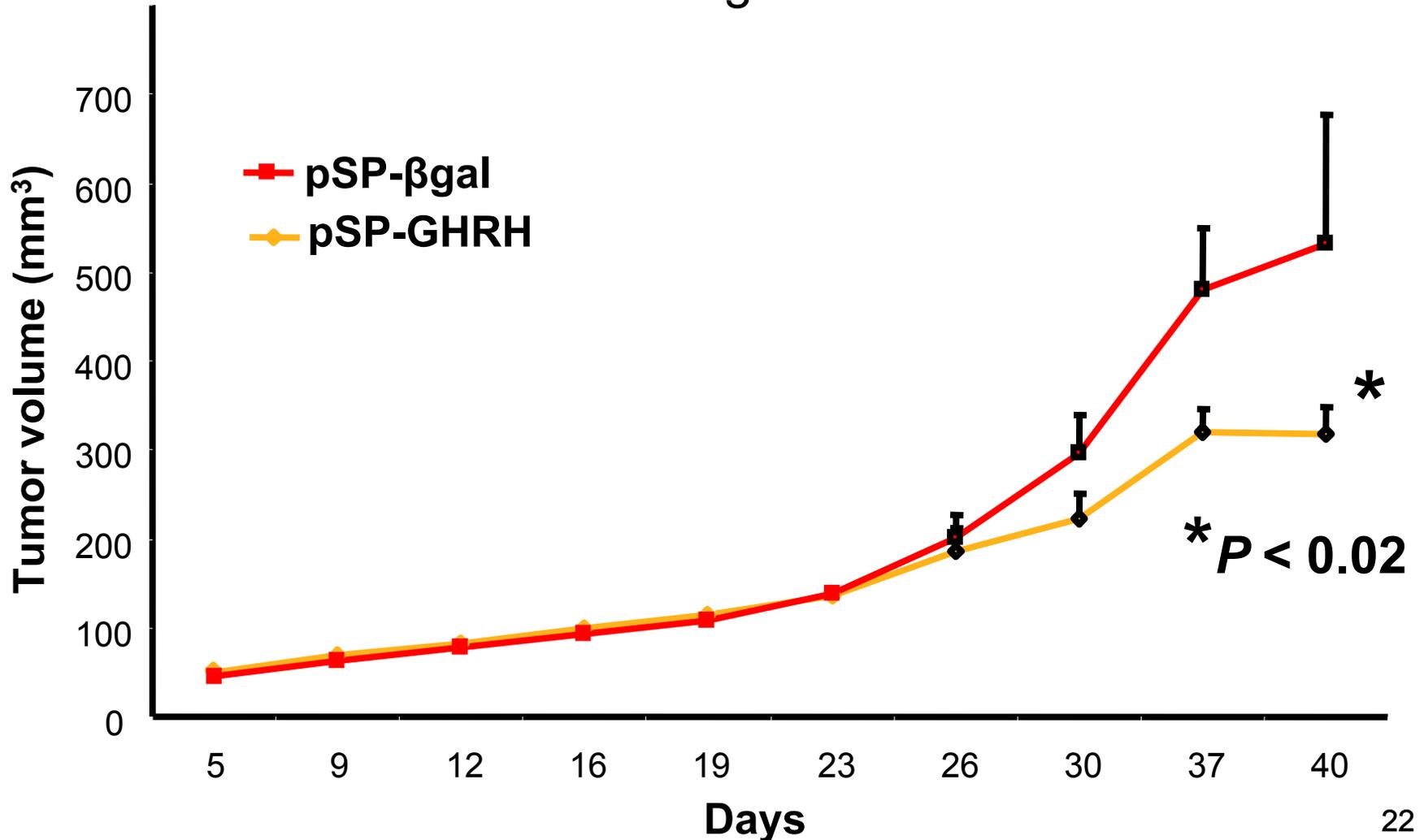
- GHRH plasmid + EP in mice significantly increased serum GHRH levels in treated animals compared to control
- Licensed product in Australia (LifeTide™ SW 5) – plasmid expressing pig GHRH injected IM + EP in sows increases survival of piglets

GHRH effects on tumor growth

- Published literature on increased growth/risk of cancer associated with GHRH/GH therapies is inconclusive:
 - ***Acromegalic patients have 10-1000 fold increase levels of GHRH/GH/IGF-I – no increased incidence of cancer with the exception of colon carcinoma (increased incidence of colonic polyps)***
 - Epidemiological studies in recipients of GH for congenital deficiencies in GH or GHRH secretion – no convincing evidence of increased risk of cancer
- Our pre-clinical data in mice with implanted tumors indicate decreased tumor growth in plasmid GHRH +EP treated animals (Khan et al Cancer Gene Ther 2005)

Tumor volume is reduced by GHRH treatment

Constitutively active GHRH plasmid 40% reduction in tumor growth



GHRH effect on tumor growth (cont'd)

- In dog model with spontaneous malignancies, GHRH plasmid + EP was not associated with accelerated tumor growth
- Ghrelin, stimulator of GH and IGF-I, in clinical trials in cancer patients to treat cachexia. Well tolerated.

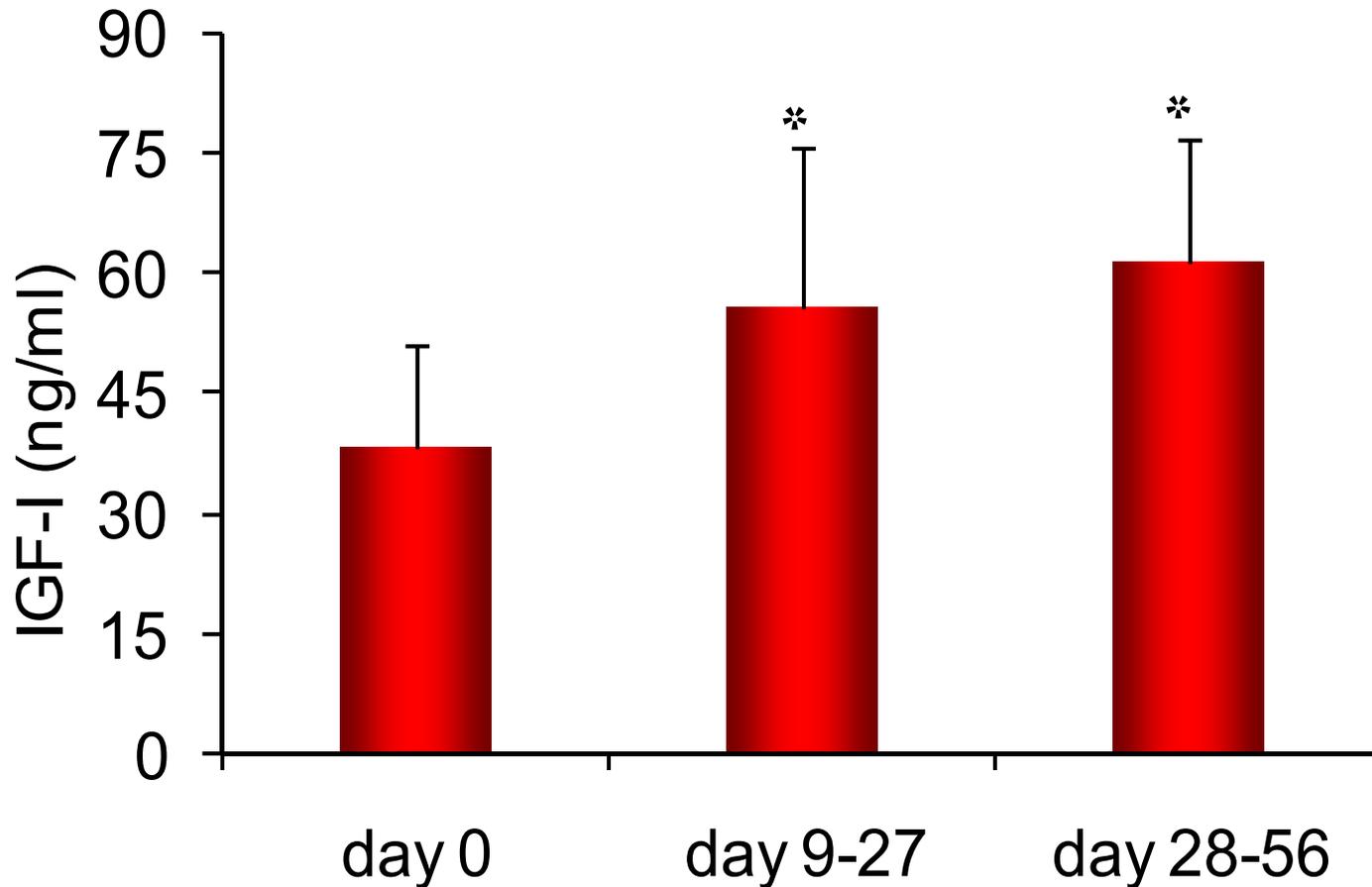
Plasmid Persistence vs. GHRH Expression

- Animal studies indicated persistence of ~ 3-6 months based on biodistribution studies;
- Difficult to directly assess expression since biological effects of therapeutic GHRH increase muscle mass resulting in improved innate production of IGF-I.

Notable changes to Informed Consent

- Patients advised to use effective birth control for 1 year after study drug administration
- Added “Another possible risk includes tumor progression”
- Added edema and arthralgias
- Other changes as requested by RAC/FDA reviewers

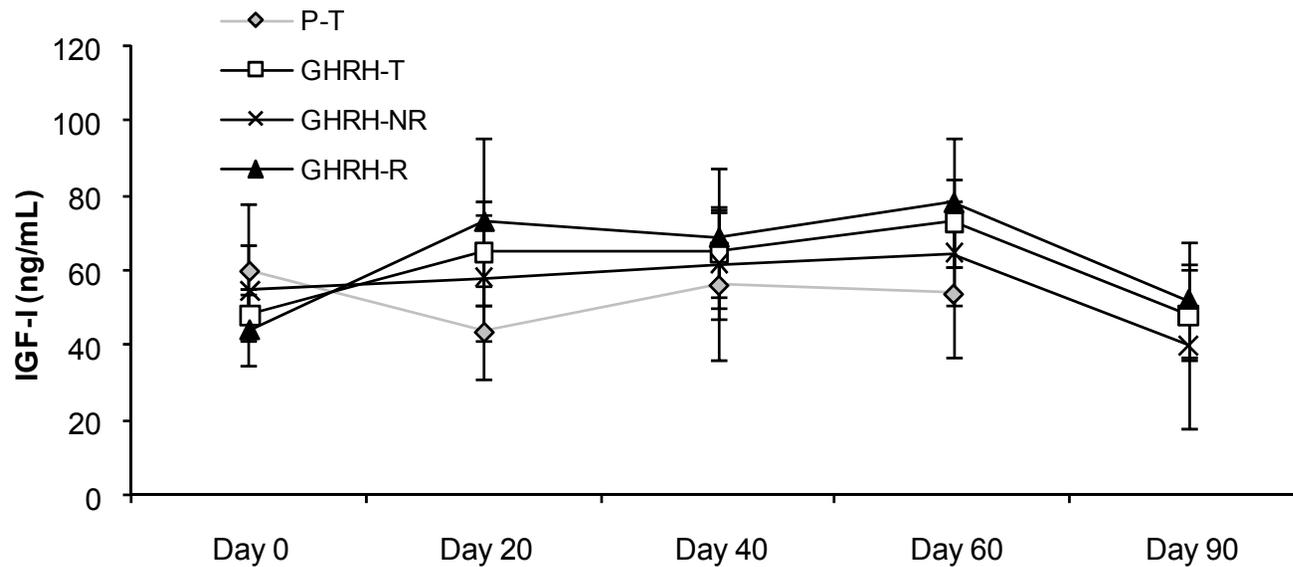
IGF-I Levels in GHRH-Treated Dogs



75% of dogs had increases of 21 to 120% in IGF-I levels compared to baseline.

Normal IGF-I level in dogs is 50 to 120 ng/ml.

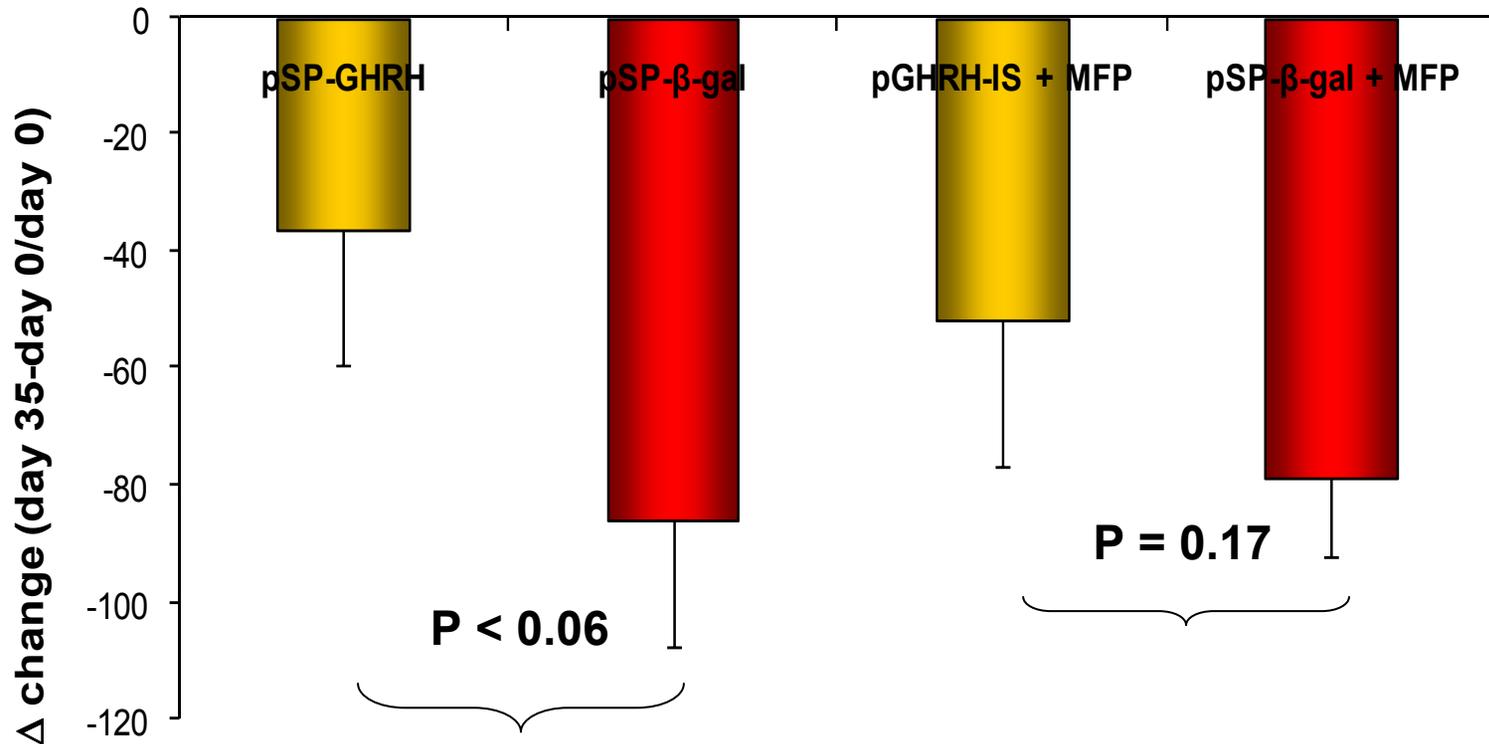
Serum insulin-like growth factor-I (IGF-I) levels in GHRH-T, GHRH-R, GHRH-NR and placebo treatment dogs.



	Day 20/0	Day 40/0	Day 60/0	Day 90/0
P-T	-27.0176	-6.29042	-10.1422	0
GHRH-T	34.12726	34.44362	50.93663	0
GHRH-NR	6.538116	12.9354	18.38617	-26.9423
GHRH-R	66.05894	56.30617	77.55961	18.57597

Percent change vs. baseline

IGF-I levels in plasmid GHRH-treated tumor-bearing mice and controls



**IGF-I levels are maintained during cancer cachexia
in GHRH-treated tumor bearing mice**