PROCOLLAGEN C-PROTEINASE ENHANCER (PCPE) BIOMARKER FOR BONE Disease

Shlomit Mesilaty, Ido Wolf & Anikster Yair, Sheba Medical Center, Israel

Categories	Biomarker Diagnostic tool for management of bone diseases
Development Stage	Efficacy from bone metastasis patients
Patent Status	Granted
THM Reference	2008052

Background

Biochemical markers of bone turnover provide clinically useful evidence of the normal and pathologic processes in the skeleton. Bone is primarily comprised of collagen-I (>90%). The rate limiting enzymatic activity of collagen-I formation is the proteolytic processing of procollagen C-propeptide. Procollagen C-proteinase Enhancer (PCPE), the target biomarker of our innovation, regulates the rate at which collagen-I formation is limited. PCPE is expressed during different phases of osteoblast development and its isoforms can be measured in different body fluids. PCPE isoforms are cell specific and deviation from normal pattern correlates with pathological stats of the bone.

The Need

structure or strength), therapy assessment (prevention side effect of bisphosphonate related osteonecrosis of the jaw), anabolic drugs development, etc.

Bone disease refers to the medical conditions which affect the bone and make it weak and prone to fractures. Bone diseases can be generally divided to four main groups-

Non-neoplastic diseases of bone	**Bone metastasis**
a. Osteogenesis imperfecta - Bone Marrow defect b. Osteopetrosis c. Paget disease of bone d. Fibrous dysplasia e. Cherubism	a. Breast cancer (75%) b. Prostate (75%) c. Lung (40%) d. Multiple Myloma

f. Florid osseous dysplasia	
Bone tumors	**Growth and aging bone disease**
a. Central giant cell reparative granuloma	a. Osteoporosis and osteonecrosis of the jaw
b. Ossifying and cementifying fibroma	b. Premature bone diseases
c. Ewing sarcoma	
d. Osteogenic sarcoma	
e. Chrondosarcoma	
f. Multiple myeloma	
g. Histiocytosis X	
(Langerhans' cell granulomatosis)	

Currently our main focus is on three major applications including bone health - Osteoporosis, Cancer - bone metastasis and bone cancer, Side effect of medications - bisphosphonate related bone necrosis (jaw osteonecrosis).

Bone metastasis diagnosis is performed today mainly by using Radiographs. A plain radiography is very specific but sensitivity is low (44-50%) because metastatic lesions may not appear on X-ray at initial stages. Lesions up to 1cm might go undetected, while more than 50% of trabecular bone must be destroyed before it will be evident on film. Medullary lesions are more difficult to detect than lesions in cortical bone because of the limited contrast in trabecular bone. Osteolytic lesions appear as a darker hole in the gray-white bone image; osteoblastic lesions appear as spots that are whiter than the bone around them.

The sensitivity of *CT* for the diagnosis of bone metastases ranges from 71-100%. CT produces images with excellent soft tissue and contrast resolution. Bone destruction and sclerotic deposits are usually clearly shown and any soft tissue extension of bone metastases is easily visualized. CT is particularly useful to localize lesions for biopsy.

MRI is required to diagnose spinal cord compression and is useful in imaging bone marrow to assess involvement by the tumor. The sensitivity ranges from 82-100% and its specificity ranges from 73-100%.

Positron emission tomography (PET) detects the presence of tumor directly by quantifying metabolic activity. It is superior to bone scintigraphy in the detection of bone metastases from lung cancer (sensitivity 92%, specificity 99%), and from BC (sensitivity 95%, specificity 94%).It has lower accuracy in renal and prostate cancer bone metastasis because they are slow growing (so, the uptake of 18-fluorodeoxyglucose is low). PET permits earlier diagnosis of bone metastases in MM, showing bone resorption sites undetected with conventional diagnostic

methods. In addition, it can reveal metastatic

Potential Applications

Current application for Quantitative kit for PCPE isoforms:

a. Diagnostic marker for OP

b. Predictive marker for BPONJ

c. Diagnostic marker for Bone Metastasis

d. Early marker for Osteosarcoma

e. Diagnostic marker for Premature Newborn bone diseases

f. Marker for tracking osteoblastic differentiation of mesenchymal Stem Cell

Quantitative kit for PCPE isoforms using an AB SCIEX Triple Quad or QTRAP® System

The kit will contain:

1. **GlycoPeptide standards** for PCPE I1,I2,I3 and I4 (optional I0 and I5 and I6)

2. Reagents, buffers and protocol for sample preparation:

2.1 **PCPE isoforms enrichment kit** (mini column)

2.2 **PCPE** peptide/glycopeptide mixture (denaturation, reduction, alkylation, digestion and purification)

3. **Data acquisition** method for LC-MRMs

4. **Processing methods** for isoforms quantification

5. **Database** for diagnosis