Research in the Division of Endocrinology

Aims & Objectives

- To create and publish new scientific knowledge
- To explore the practical application of theoretical knowledge and thereby improve:
  - → patient care
  - → teaching
  - → techniques, technologies, further research
- To improve insights and enrich an individual's ability:
  - → critical analysis; QC
  - → systematic, mechanistic thinking
  - → problem solving

Research Culture

OSTEOPOROSIS

DIABETES

Research Culture

OSTEOPOROSIS

DIABETES

Descriptive & Mechanistic

Research Culture

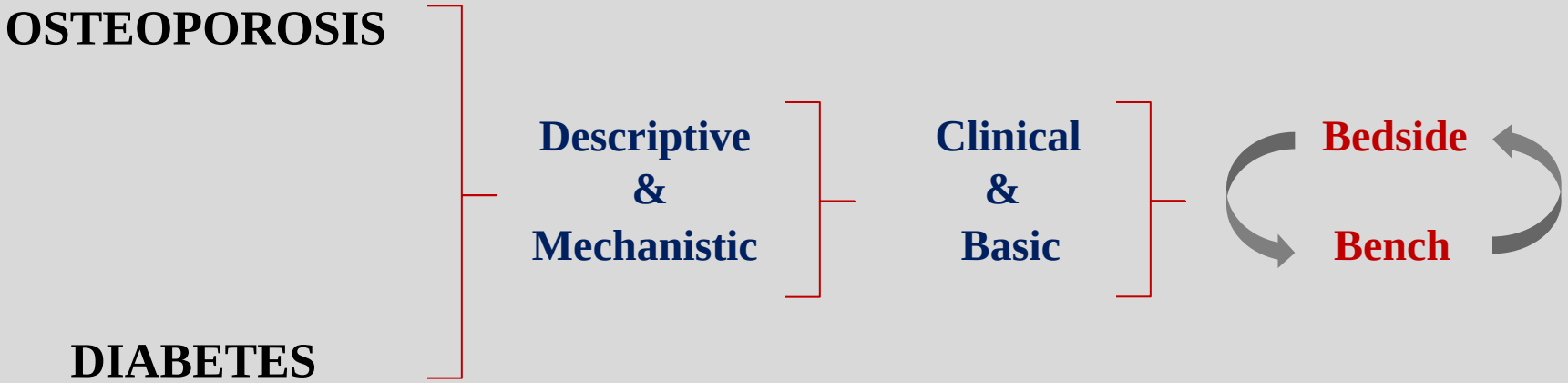
OSTEOPOROSIS

DIABETES

Descriptive & Mechanistic

Clinical & Basic

Research Culture



Examples of BB&B Research

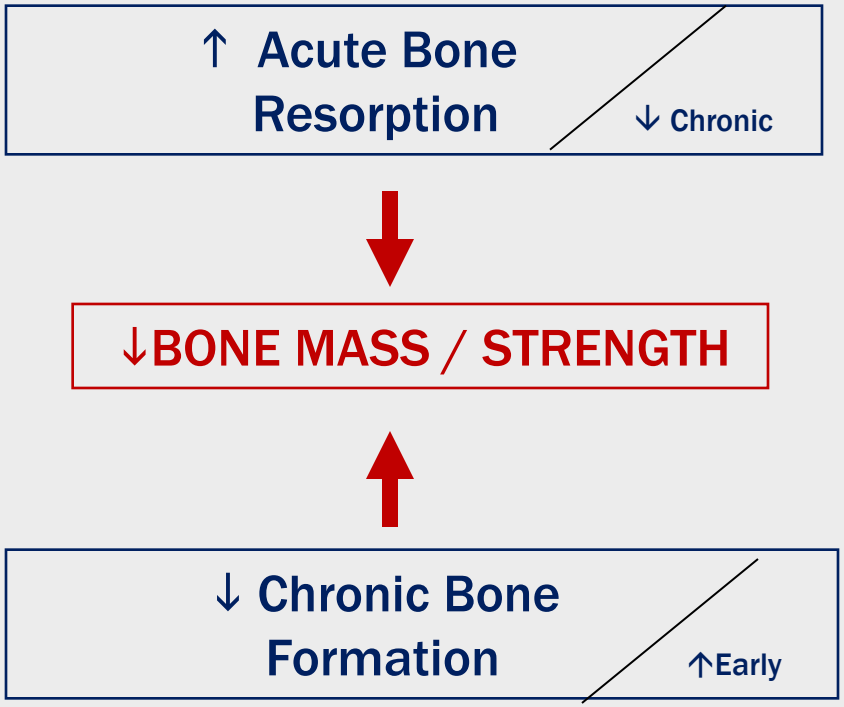
- Glucocorticoid Osteoporosis
- HIV, ARVs and Skeletal Health
- Acanthosis Nigricans
- Diabetic Bone Disease
- Dietary Protein and Bone Health
- Stress Fracture in Athletes
- Hypervitaminosis A and Bone

PREVALENCE OF STEROID INDUCED-OSTEOPOROSIS

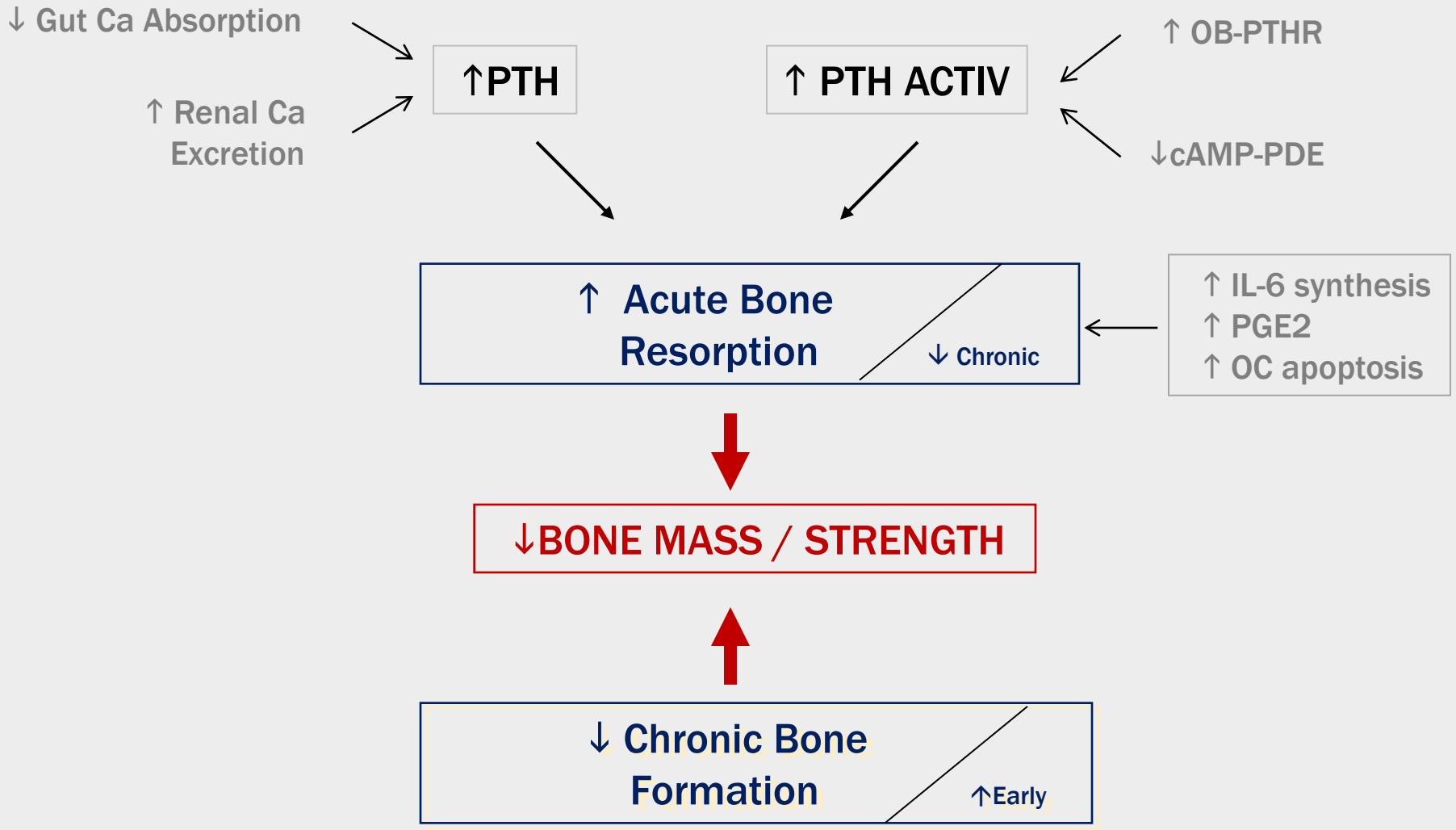
Subjects	Steroid Therapy	Non-steroid Therapy
Total	27/59 (46%)	12/51
Premenopausal	15/34 (44%)	4/24
Postmenopausal	5/11 (45%)	1/5
Males	7/14 (50%)	7/22

Nortje et al

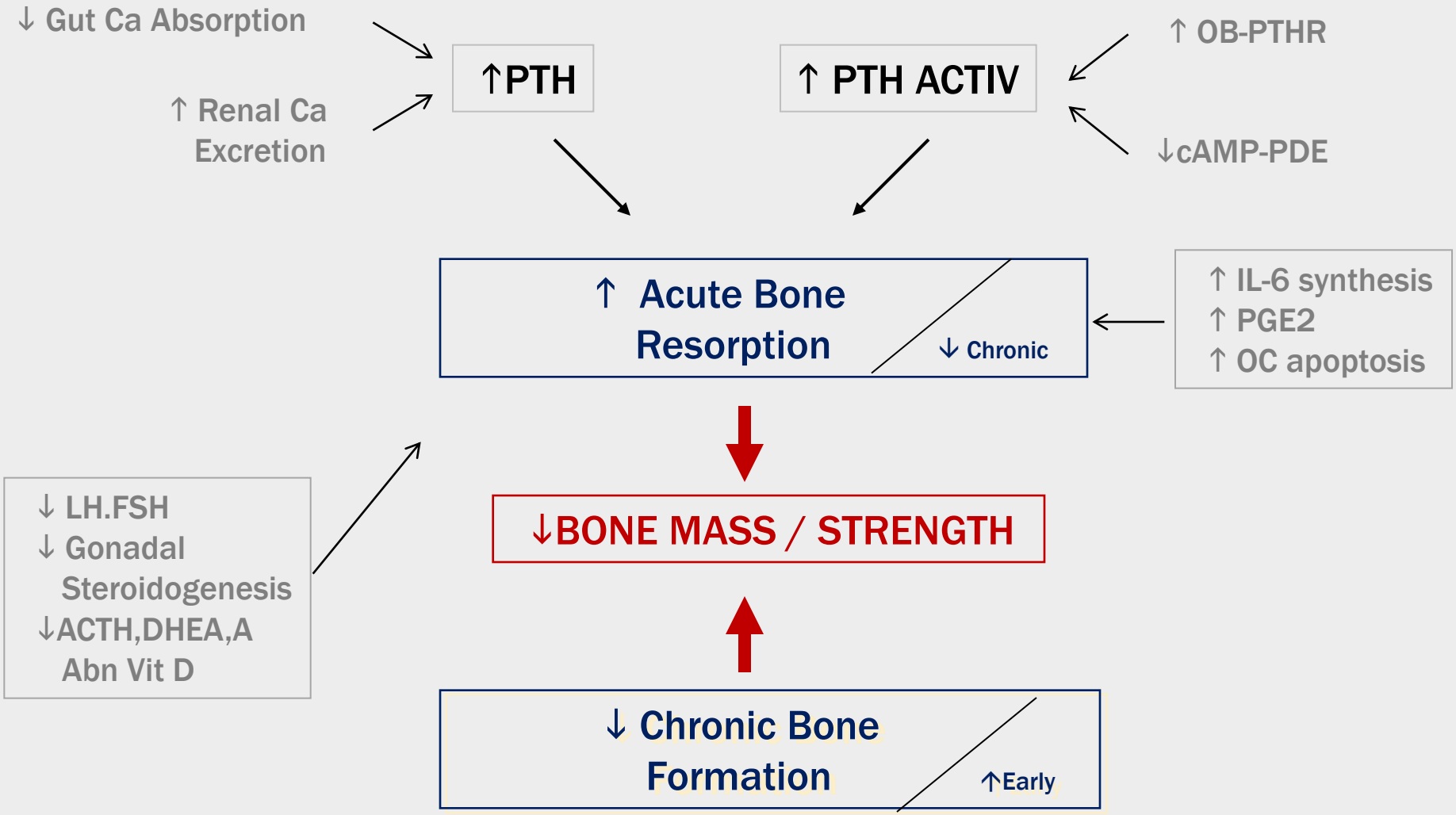
Pathogenesis of GIOP



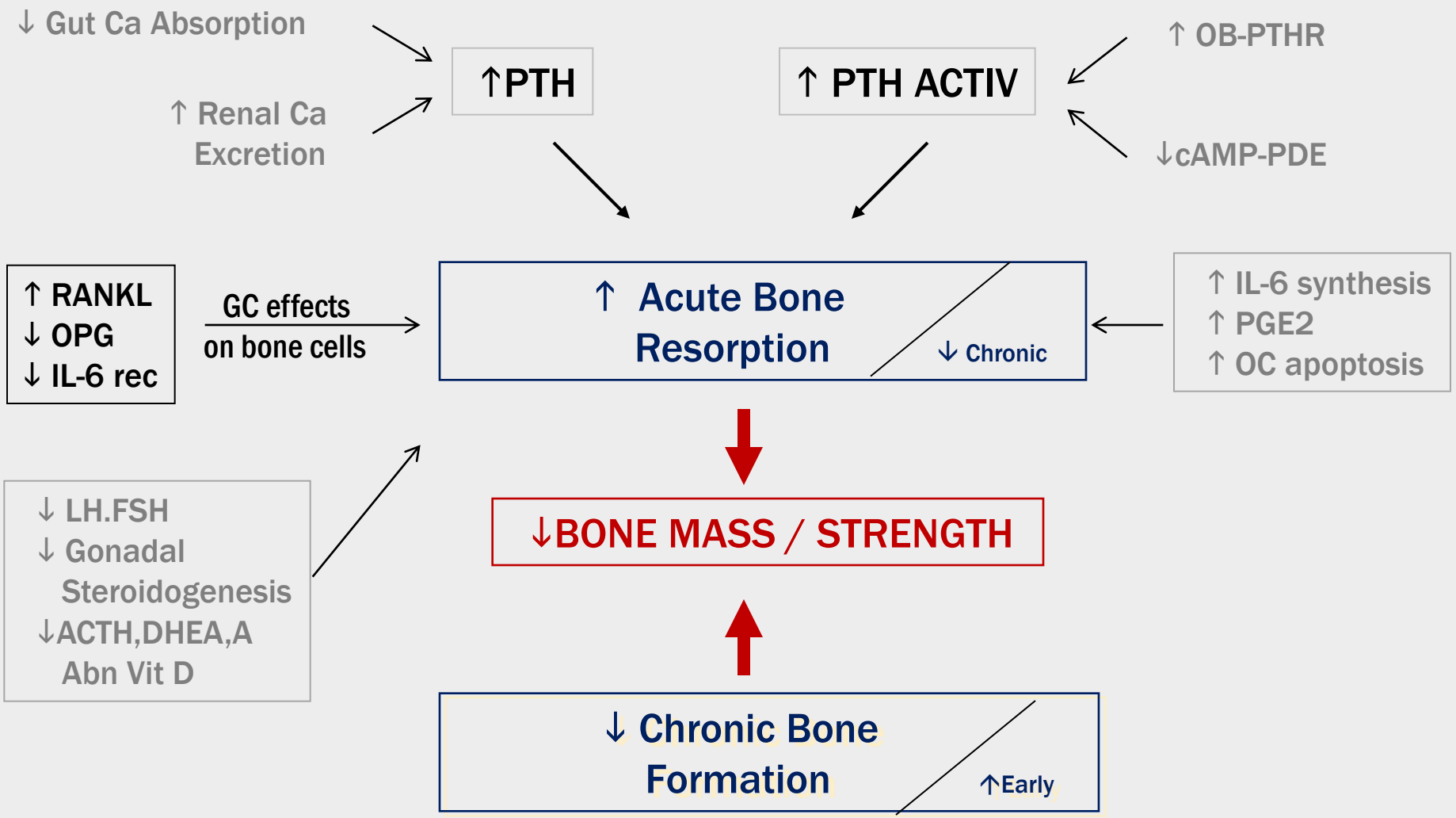
Pathogenesis of GIOP



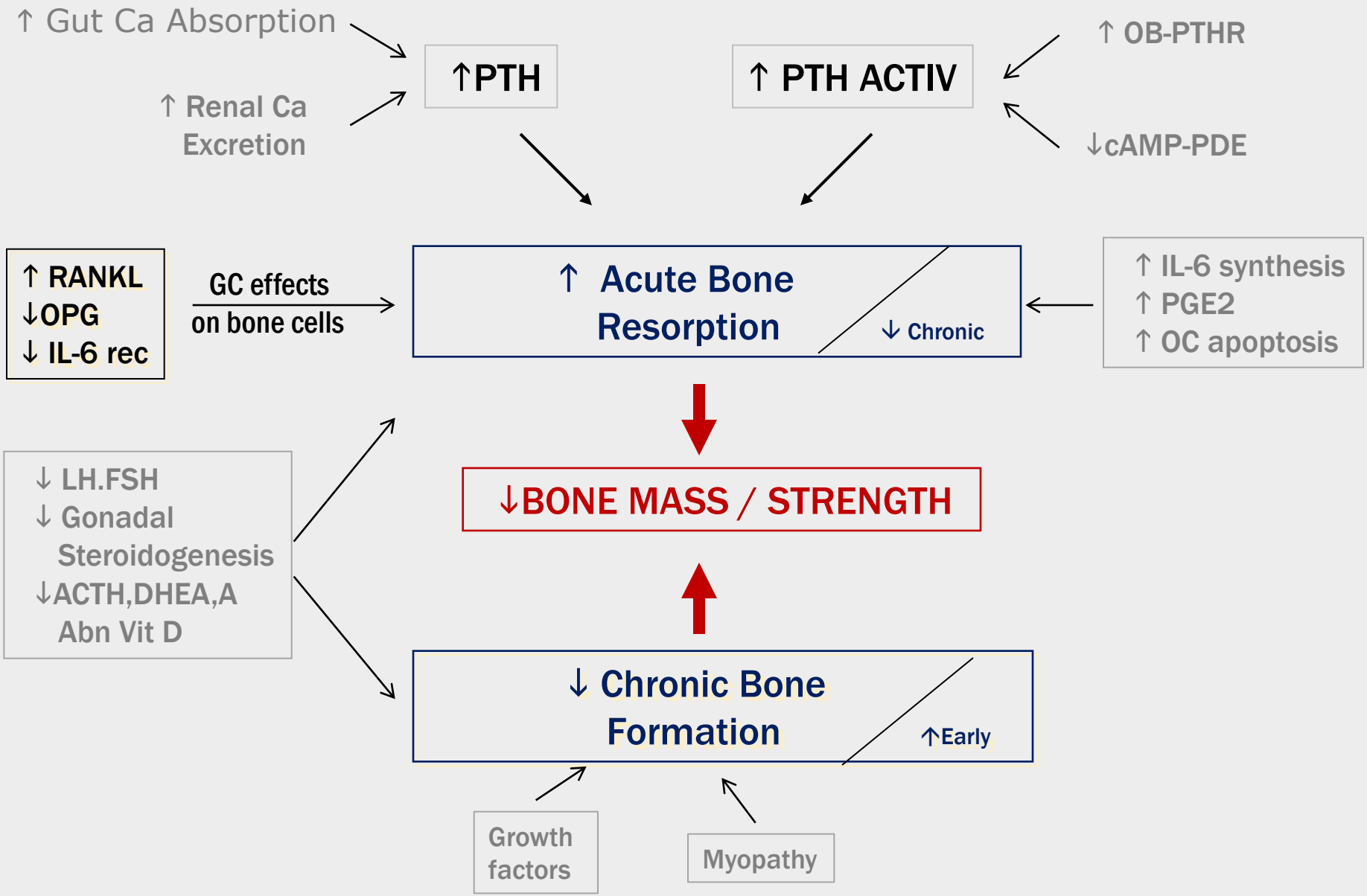
Pathogenesis of GIOP



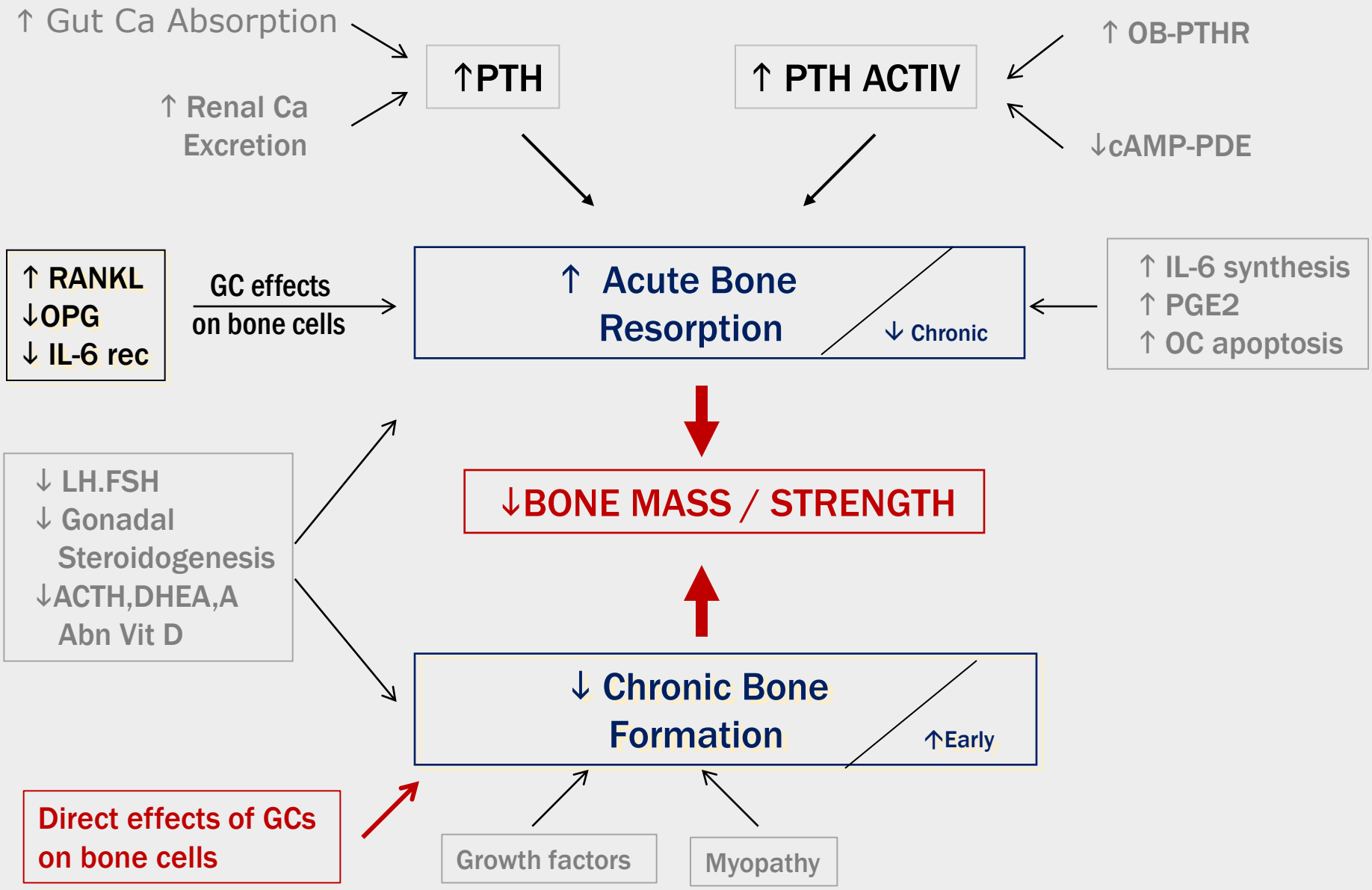
Pathogenesis of GIOP



Pathogenesis of GIOP

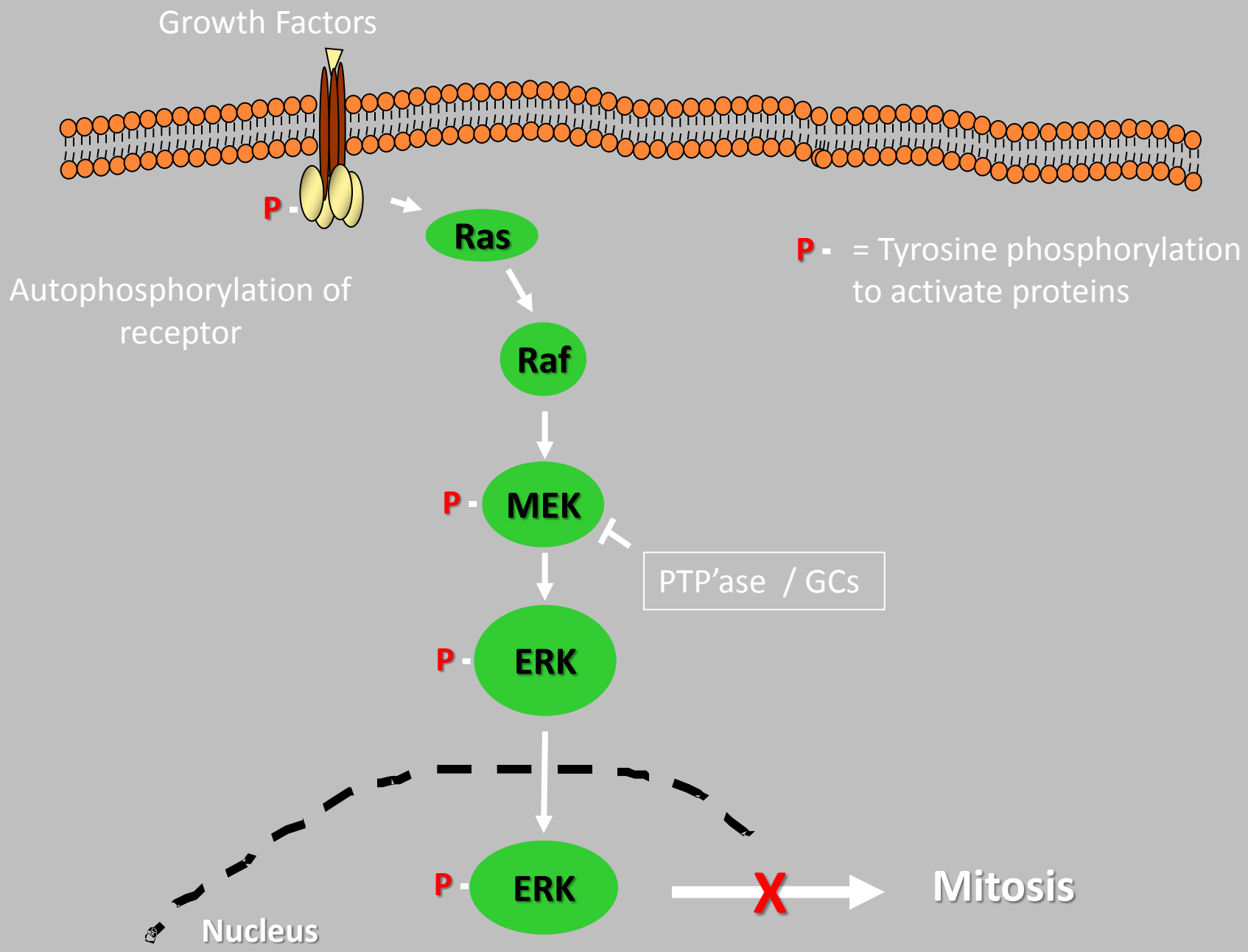


Pathogenesis of GIOP

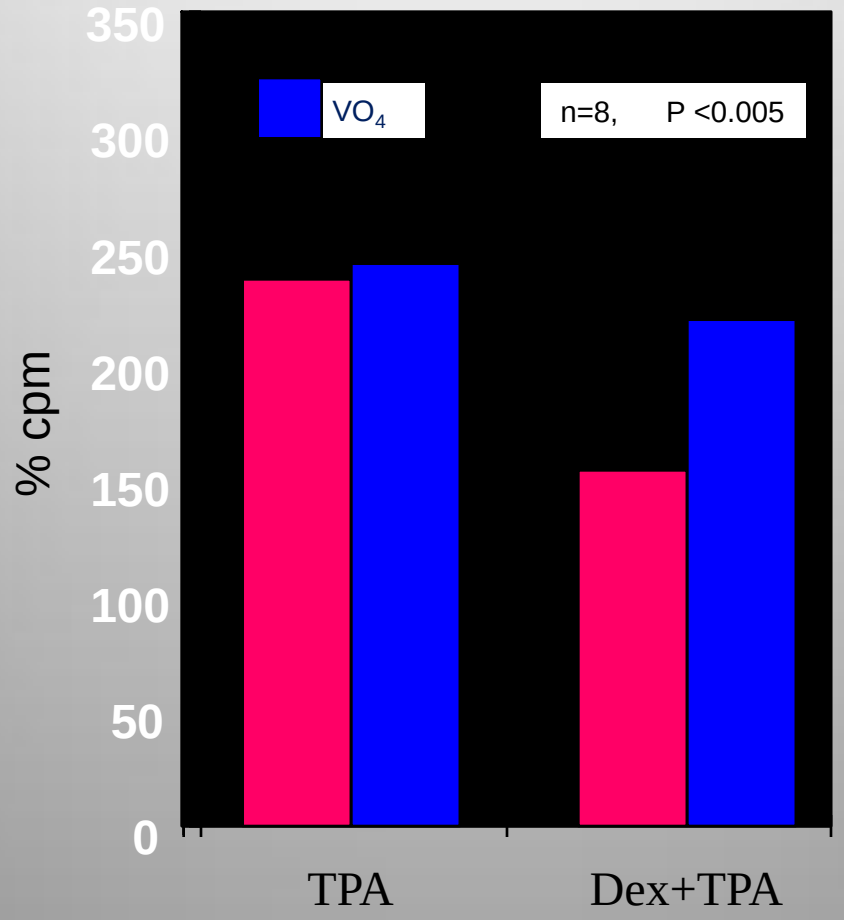


Direct effects of GCs on Osteoblasts/Preosteoblasts

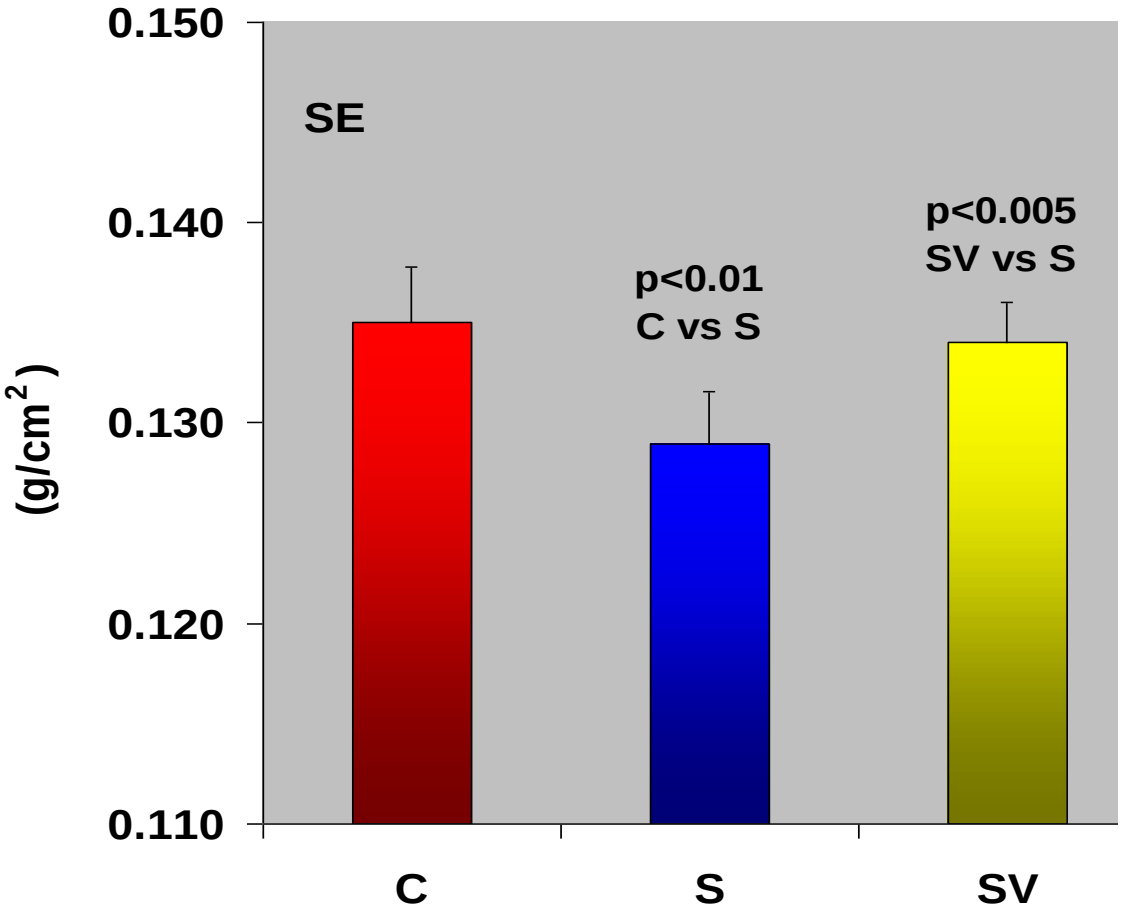
- Intracellular Signal Transduction
- Cell Fate: Proliferation, Differentiation, Trans-differentiation, Senescence, Apoptosis


Growth Factors
P -
Ras
Autophosphorylation of receptor
P - = Tyrosine phosphorylation to activate proteins
Raf
P -
MEK
PTP'ase / GCs
P -
ERK
P -
ERK
X
Mitosis
Nucleus

Osteoblast Proliferation

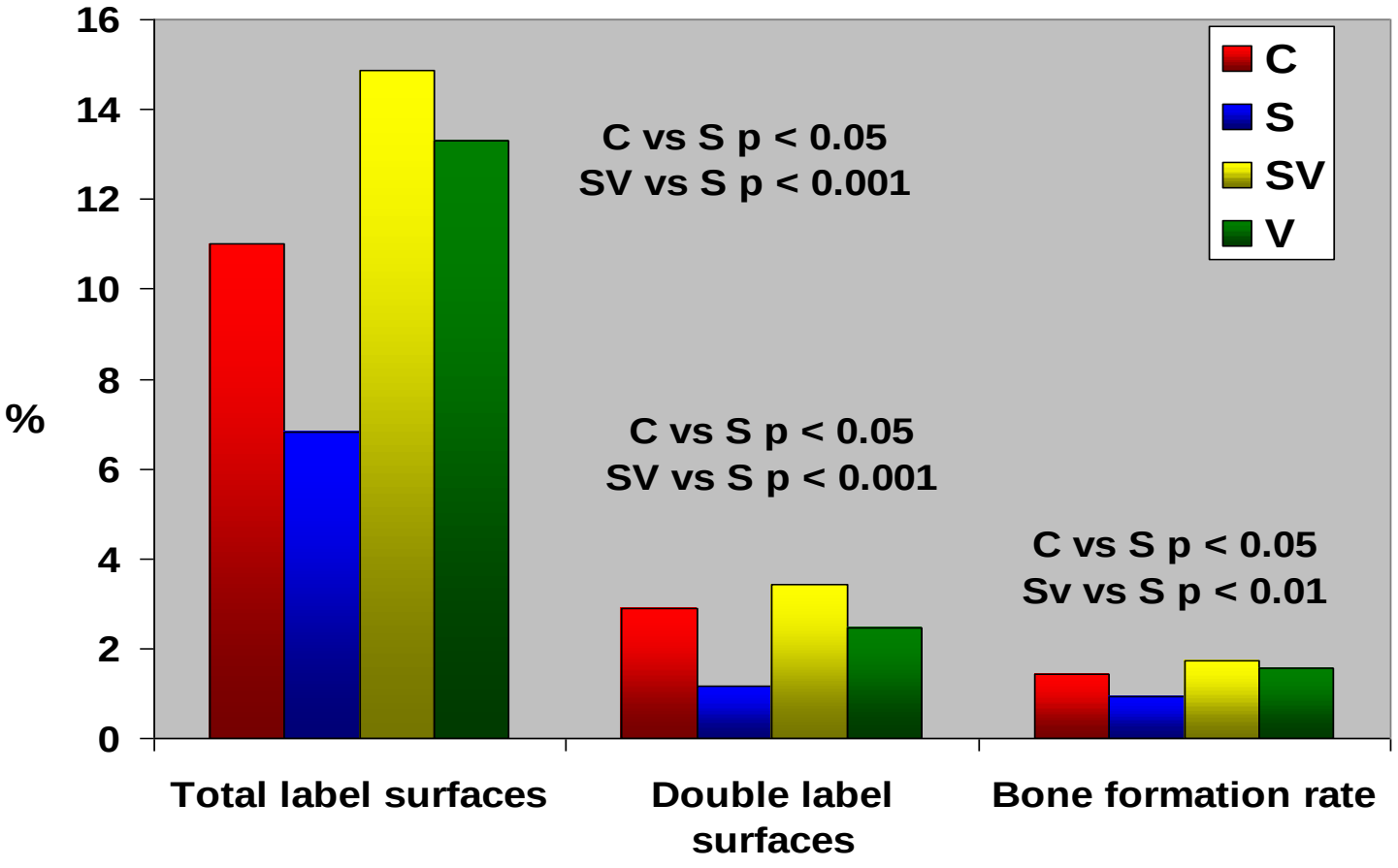


Bone Mineral Density (g/cm^2)



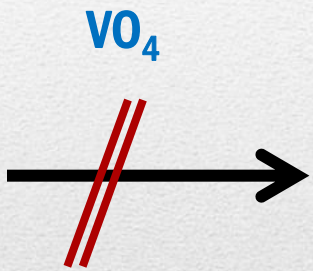
Eagar et al

Dynamic Formation Parameters



Eagar et al

Glucocorticoids



↑ Tyr phosphatases

↓ MAPK/ERK activity

↓ Ob proliferation

↓ Bone formation

↓ BMD

↓ Bone strength

MKP-1 induction correlates with ERK dephosphorylation

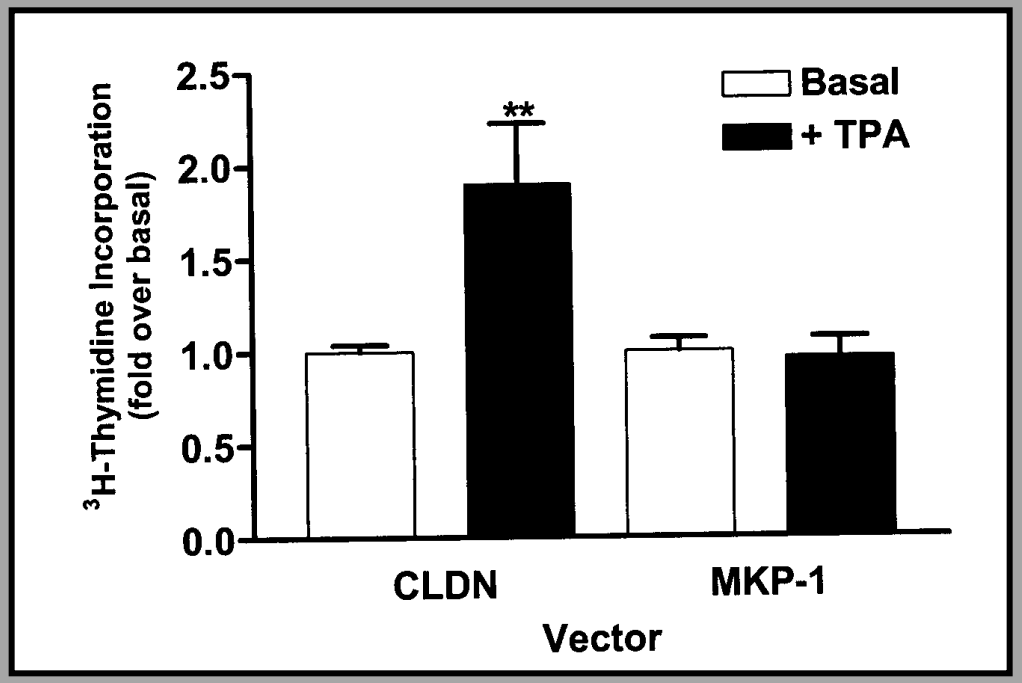
10% FCS

1μM Dex - 7h

MKP-1 →

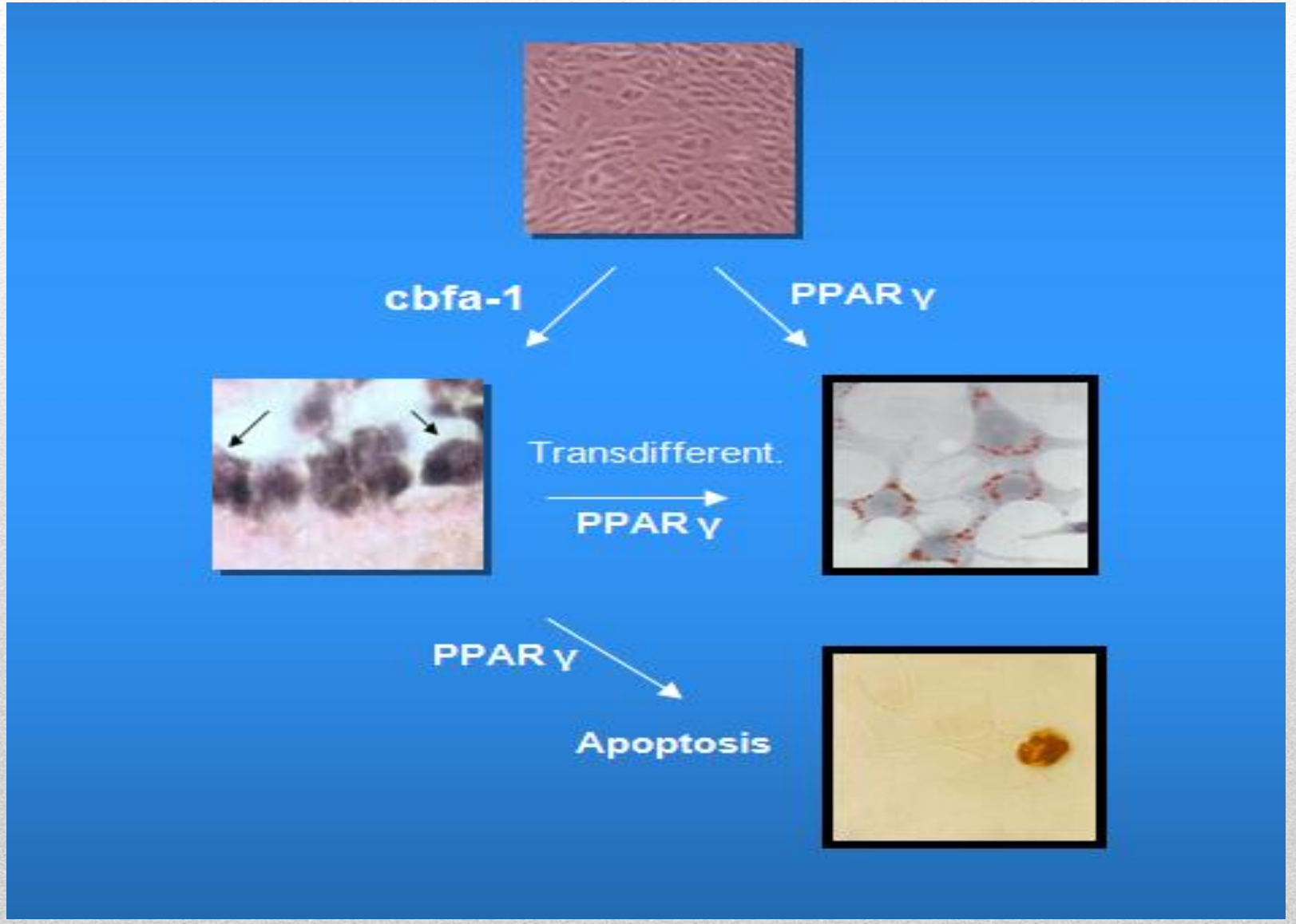
P- ERK ⇉

MKP-1 overexpression in MG-63 human osteoblasts abrogates proliferation

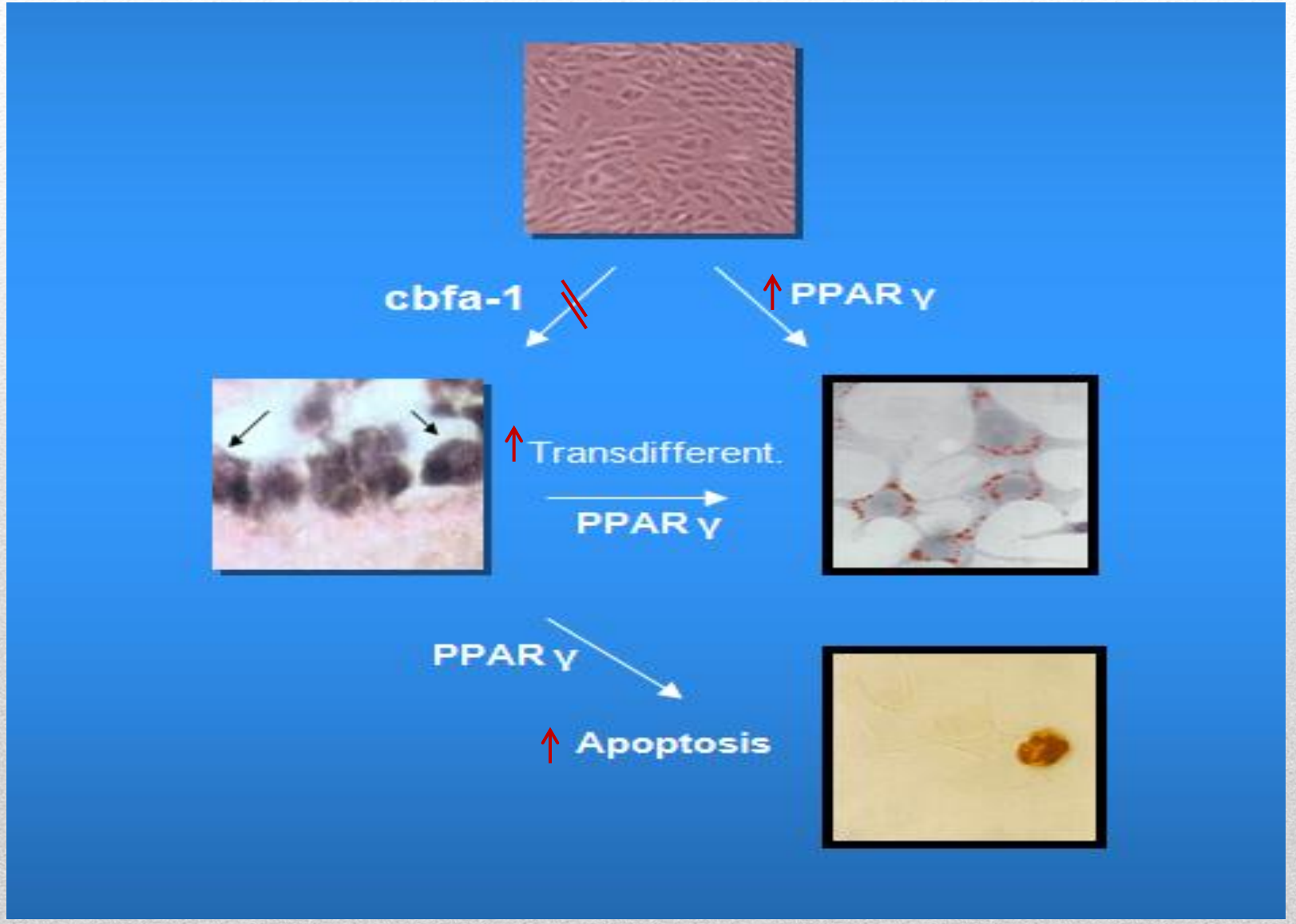


Hulley et al 2007

Cell fate and the bone – fat axis



Influence of GCs on cell fate and the bone – fat axis



Examples of BB&B Research

- Glucocorticoid Osteoporosis
- HIV, ARVs and Bone
- Acanthosis Nigricans
- Diabetes and Skeletal Health
- Dietary Protein and Bone Health
- Stress Fracture in Athletes
- Hypervitaminosis A and Bone

Causes of a low BMD in HIV

- Direct effects of the Disease
- Associated Osteoporosis Risk factors
- Effects of HIV Treatment

- *Innes et al*
- *Andersson et al*

- *Eagar et al*

ARVs & Osteoblasts

- Direct infection and apoptosis

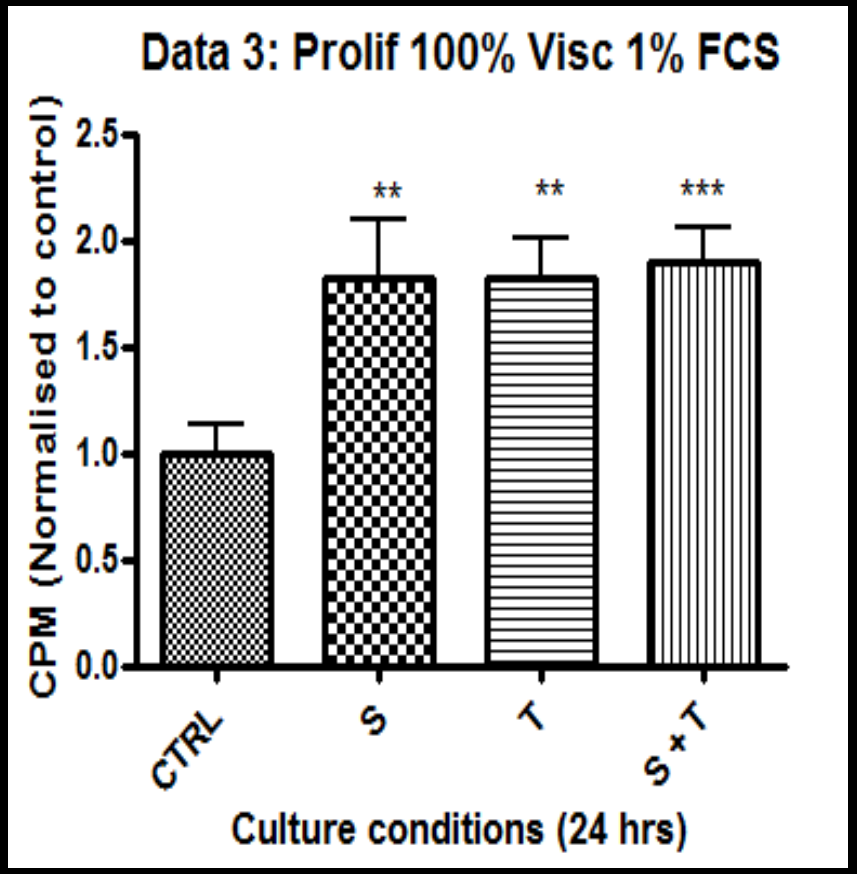
Wang et al AIDS RHV 2002

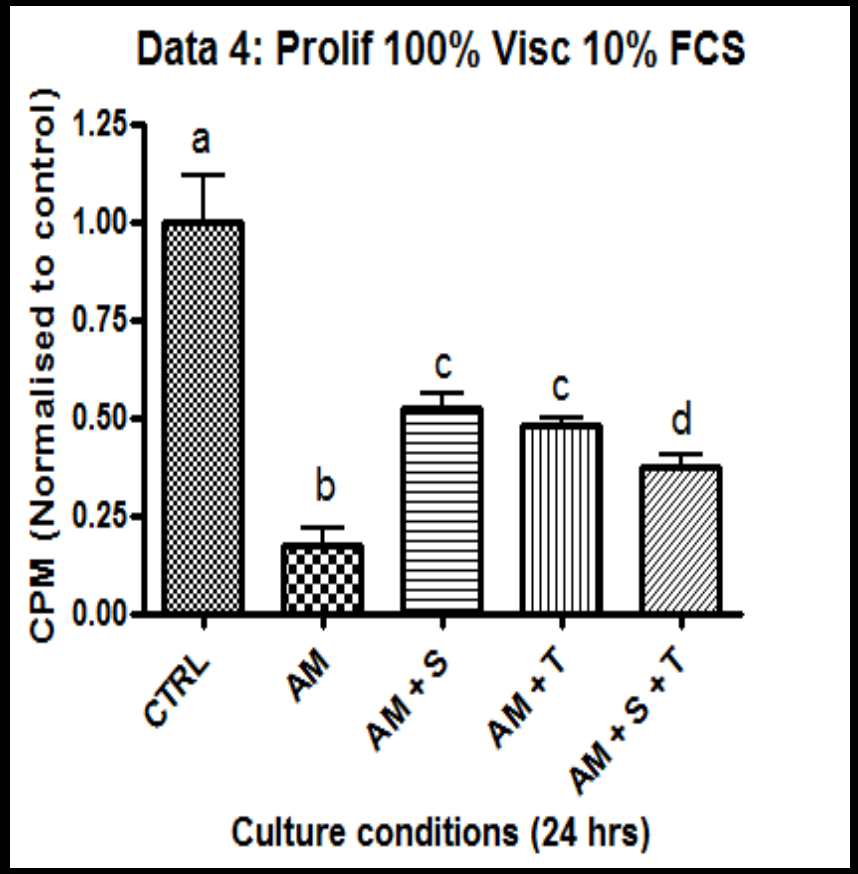
- Para / autocrine effects of TNF-α on osteoblast apoptosis

Gibellini J Med Virol 2008

- MSC → Adipocytes
  - ⇏ Osteoblasts

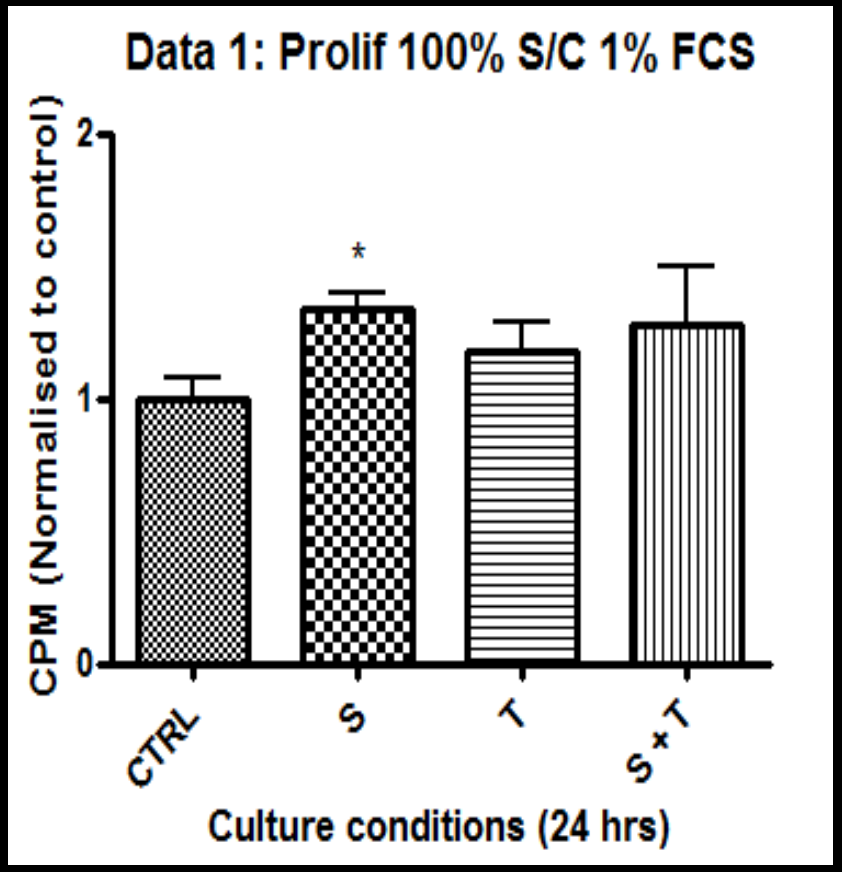
Proliferation of ADSC from Visceral Depots

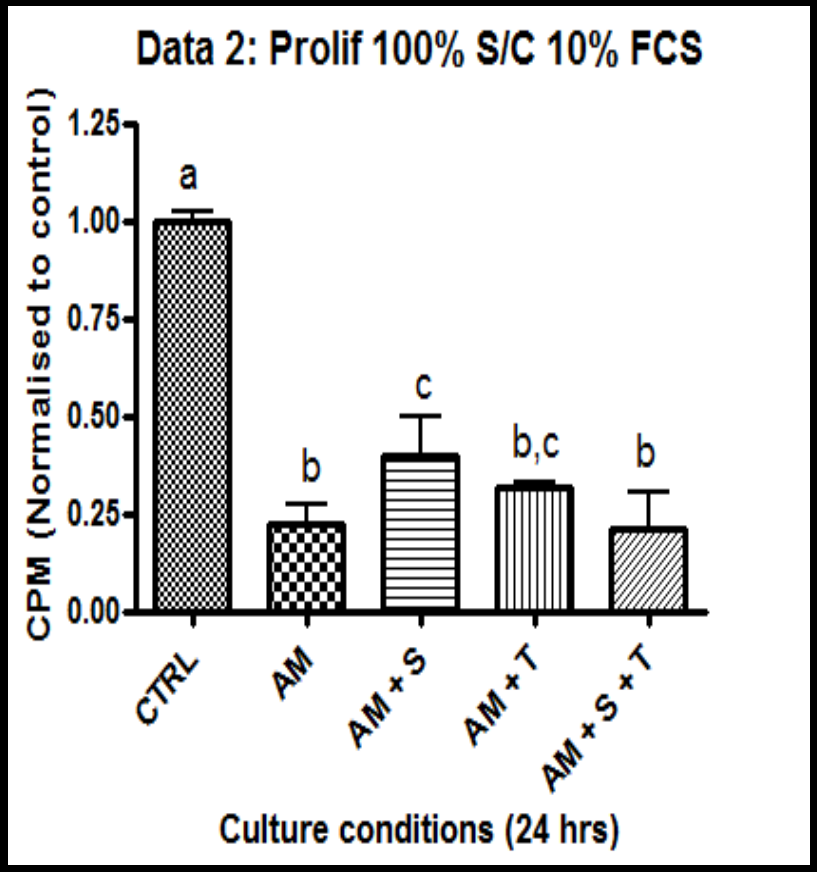




Greyling et al 2012

Proliferation of ADSC from Subcutaneous Depots





Greyling et al, 2012

Examples of BB&B Research

- Glucocorticoid Osteoporosis
- HIV, ARVs and Bone
- Acanthosis Nigricans
- Diabetes and Skeletal Health
- Dietary Protein and Bone Health
- Stress Fracture in Athletes
- Hypervitaminosis A and Bone

THE PREVALENCE AND CLINICAL SIGNIFICANCE OF ACANTHOSIS NIGRICANS IN DIABETIC AND NON-DIABETIC WOMEN OF MIXED ANCESTRY

Hoffman et al

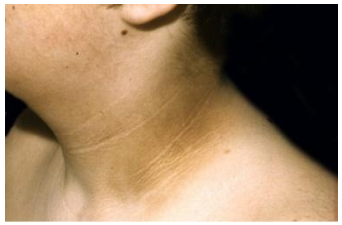
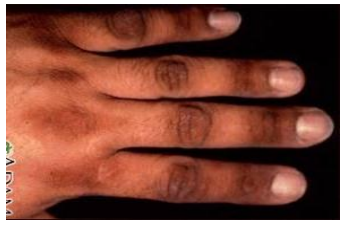
4 Phases of study:

1. Determine prevalence in adult female population and association with plasma glucose obesity and hypertension (385 patients)
2. Determine prevalence of AN in diabetic females and association with components of the metabolic syndrome, micro- and macrovascular complications (250 patients)
3. Determine association of AN (+) T2DM patients with the degree of insulin resistance and presence and distribution of body fat, PCOS and NAFLD (85 patients)
4. Investigate the cellular pathway activated in AN patients

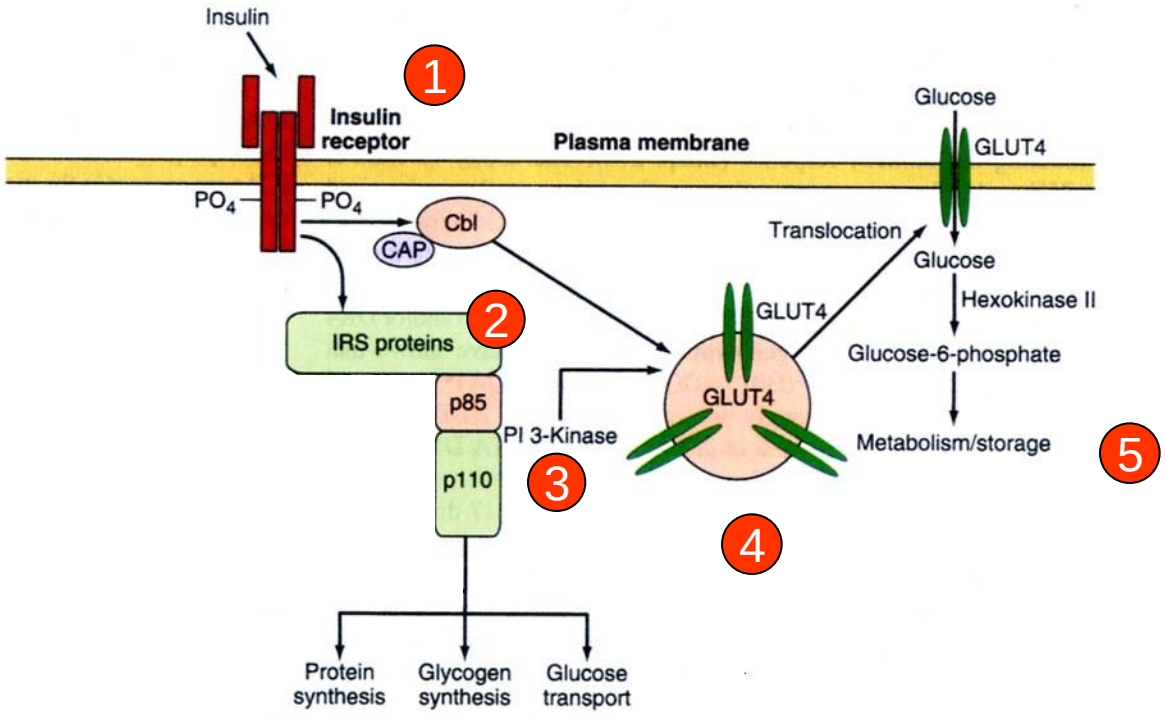
Progress

- Approved by Ethics Committee; HC funding
- Submitted for PhD application
- Phase 1 recruitment completed (ready for statistical analysis)
- Funding obtained for phase 4

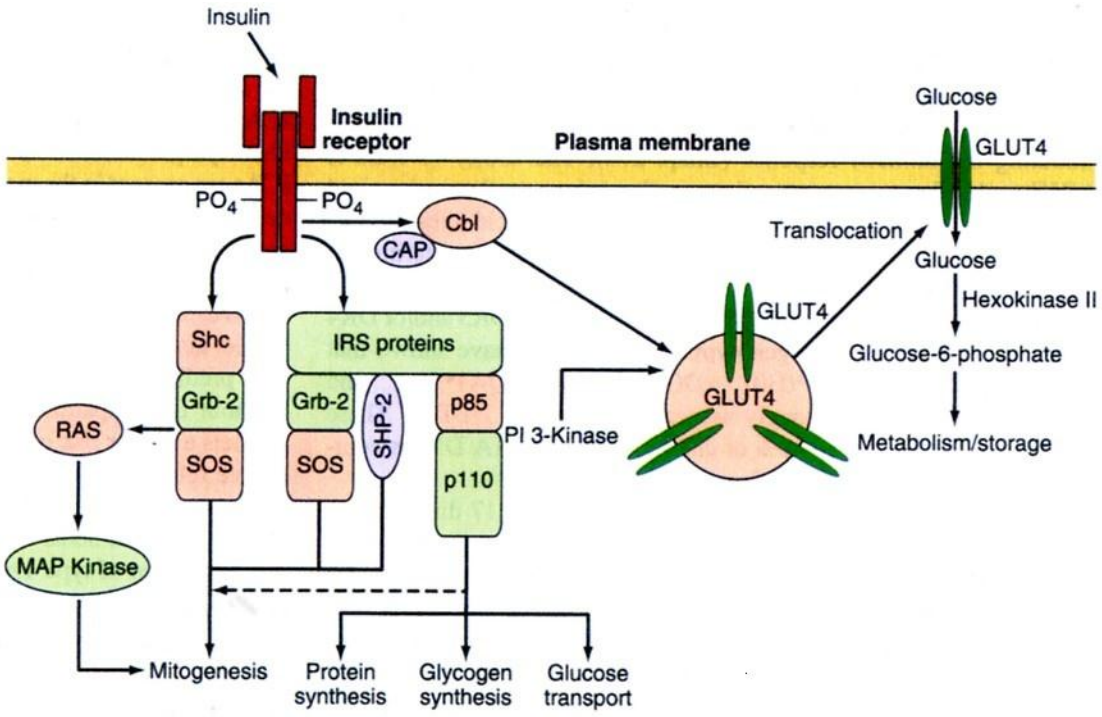


Insulin Resistance: Defects in Signalling



Intracellular Insulin Signalling



Mitogenic **Metabolic**

AN: Research

Phase IV

To assess possible *pathophysiological mechanisms* involved in the development of AN in patients with T2DM

- Standard punch biopsy from area of AN, from area of apparent normal skin, from control subject
- Separate epidermis from dermis by dispase treatment; liberate keratinocytes from epidermis with trypsin; plate on a collagen-coated tissue culture petri.
- Use isolated keratinocytes and fibroblasts to assess:
  - ***Cellular proliferation*** (*ex vivo* in absence of potent mitogens, and *in vitro* following treatment with 20% FBS or insulin)
  - ***Rate of apoptosis*** (TUNEL staining)
  - Contribution of the ***MAPK/ERK pathway*** in mediating the cellular proliferation of these cell (inhibitors like UO126, phospho-ERK etc)

Completed Studies

OSTEOPOROSIS

- Bone and mineral metabolism in neonates *(NB, PhD)*
- Clinical risk factors for the development of osteoporosis *(RB, PhD)*
- Risk factors for hip fractures *(DvP, PhD)*
- Body fat distribution and OP
- Endemic fluorosis
- Osteoporosis in men
- Season, latitude and Vit D activation
- Exercise induced OP in women *(KM, PhD)*
- BMD in anorexia nervosa *(RE, MSc)*
- BMD and fracture in Black and White South African women *(MC, PhD)*
- Statins and bone *(FM, PhD)*

DIABETES

- Acute phase proteins and the diagnosis of infection in DM
- Micro- and macrovascular complications of diabetes in white and mixed race populations
- The lung in DM *(MS, PhD)*
- Diabetic bone disease *(FSH MD)*
- Diabetic diarrhoea
- Lipid and lipoprotein profiles in diabetes
- Measurement of microalbuminuria in diabetes
- Measurement of serum ketone bodies in diabetes, employing a point-of-care device.

CURRENT STUDIES

OSTEOPOROSIS

- Incidence of hip fracture in four population groups in South Africa
- Molecular biology of stem cell differentiation into fat and bone cells
- Drugs and osteoporosis
  - ARV
  - AI
  - VO_4
  - GCs
  - TZDs
- Others

DIABETES

- Acanthosis nigricans
- TZDs and bone
- Diabetes in pregnancy
- Prospective audit of hyperglycaemic emergencies presenting at a tertiary level (TBAH): Prevalence and nature of KPD
- Hyperglycaemic emergencies at secondary level: Defining the metabolic crisis of DKA

Diabetes in Pregnancy

Rademan , Conradie et al

1. *Clinical patient care*

   We have established a multidisciplinary team directed at optimal tertiary management of pregnant diabetics presenting to the TBAH over the last 3 years and include a team of dedicated obstetricians, diabetologists, a dietitian and a nurse educator.

2. *Provincial Government of Western Cape Guidelines*

   Instrumental in revising guidelines for care of pregnant diabetics in the Western Cape. Directed mainly at primary and secondary care facilities and medical staff.

PROVINCIAL GOVERNMENT WESTERN CAPE
DIABETES IN PREGNANCY
Guideline for the management of diabetes and its complications from pre-conception to the postnatal period

3. *Clinical Research*

   Incidence of Type 2 diabetes mellitus in women following a diagnosis of Gestational Diabetes.

CURRENT STUDIES

OSTEOPOROSIS

- Incidence of fractures in four population groups in South Africa
- Molecular biology of stem cell differentiation into fat and bone cells
- Drugs and osteoporosis
  - ARV
  - AI
  - VO_4
  - GCs
  - TZDs
- Others

DIABETES

- Acanthosis nigricans
- TZDs and bone
- Diabetes in pregnancy
- Prospective audit of hyperglycaemic emergencies presenting at a tertiary level (TBAH): Prevalence and nature of KPD
- Hyperglycaemic emergencies at secondary level: Defining the metabolic crisis of DKA

Prospective audit of hyperglycaemic emergencies presenting at a tertiary level (TBAH): Prevalence and nature of KPD

Zane Stevens et al

Aim:

- Prospective Audit of Hyperglycaemic Emergencies presenting to TAH.
- Describe the incidence of DKA in existing type 1 and 2 patients.
- Investigate and compare the prevalence of KPD in different ethnic groups (white, black, mixed race and Indian).

Hyperglycaemic emergencies at secondary level: Defining the metabolic crisis of DKA

Francois van Zyl et al

Aim:

- To characterize hyperglycaemic emergencies at a secondary level care facility in the Western Cape (Cape Winelands East / Boland Overberg), and to
- Evaluate the use of a validated point-of-care device to measure serum ketones (β-OHB) in defining the metabolic crisis of DKA.
- Sub-analysis of patients presenting with features of ketosis-prone Diabetes (KPD).