XXI GISMO

LE NUOVE FRONTIERE DELLE MALATTIE METABOLICHE DELL'OSSO

UDINE

14 - 15 novembre 2025

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MIELOMA MULTIPLO

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Multiple myeloma

- Malignancy of bone marrow plasma cells (1% cancers, 2% of all cancer deaths)
- Median age at diagnosis: 70 yrs (~40% <65)
- Multifocal growth in the hematopoietic skeleton
- Monoclonal Ig in serum or urine
- End-organ damage at diagnosis:
    - Osteolytic lesions (up to 80-90% by X-ray), bone pain (60%), hypercalcemia
    - Anemia (>70%), immune deficiency
    - Renal insufficiency (<40%)

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Pioneering clinical records

Sarah Newbury, age 39, died 1844.

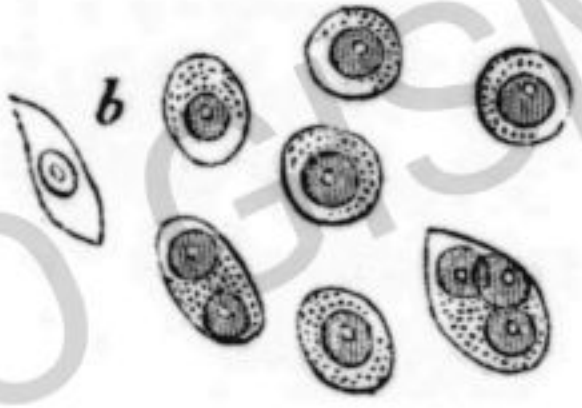
Bone pain *"just as if her thighs were being broken into a thousand pieces"*

Multiple fractures: clavicles, humeri, radius, ulna, hips.

At autopsy, cancellous sternum and femuri appeared replaced by a *"red gelatiniform substance"*.

"McBean Mollities Ossium"

Thomas Alexander McBean, died 1846
45-years old



First drawings of plasma cells (Dr. Dalrymple at McBean's autopsy).

Dr. William Macintyre, London:
*"This highly respectable tradesman was confined to his house by excruciating **pains of the chest, back, and loins**".*

Post-mortem examination found "***brittle bones***" (ribs and sternum) filled with a *"gelatiniform substance of blood-red colour and of unctuous feel".*

Dr. Macintyre notes urinary turbidity and sends a sample to a chemical pathologist in London, Dr. Henry Bence Jones

"McBean Mollities Ossium with Macintyre's Proteinuria"

Chemical pathologist Dr. Bence Jones calculated a urinary excretion of 67 g protein per day, which he judged a relevant feature of this previously unreported disease:

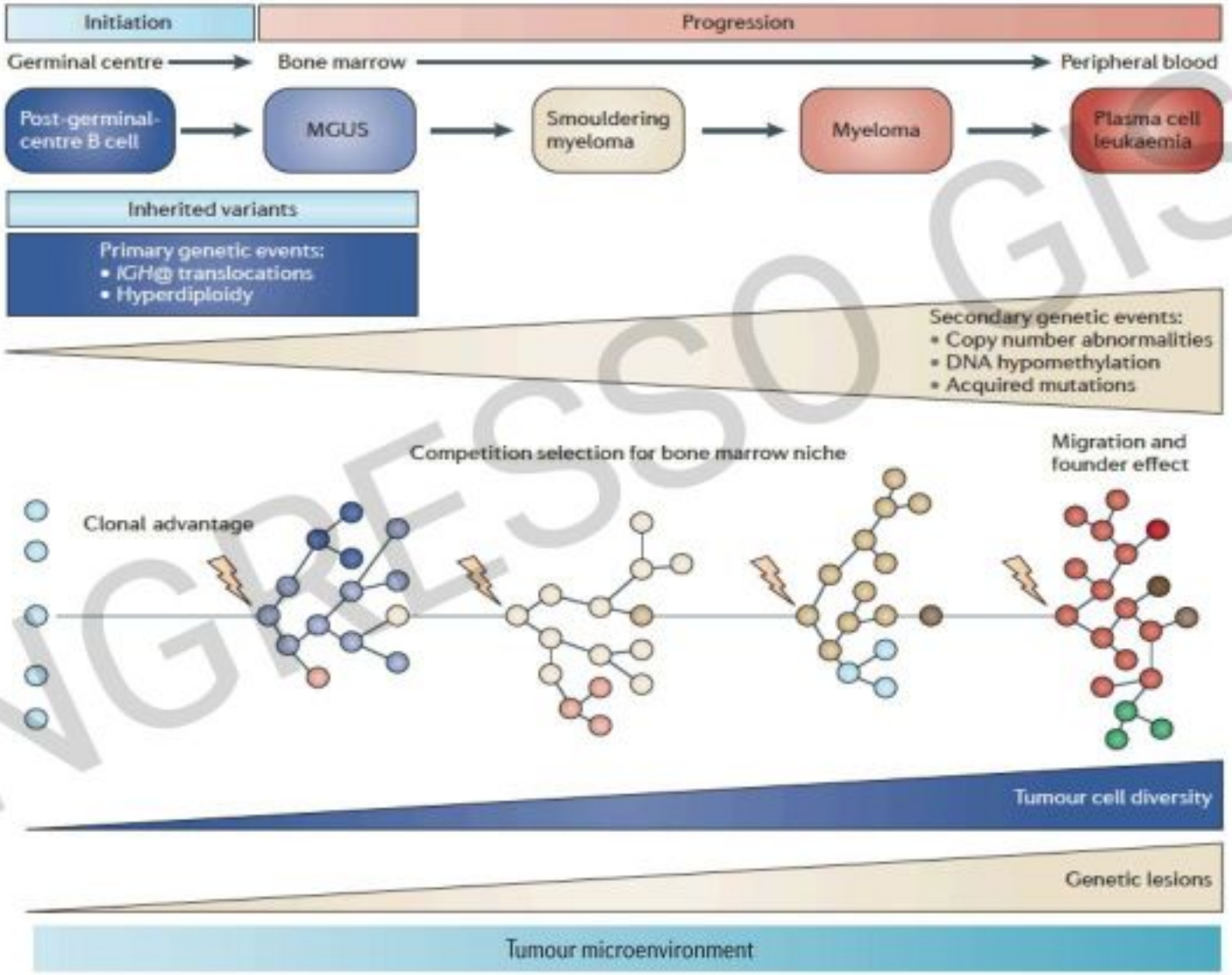
"I need hardly remark on the importance of seeking for this proteinuria in other cases of mollities ossium"

Henry Bence Jones, 1813-1873

- 1873: J. Von Rustitzky provides the first systematic description of 8 distinct lesions in a patient, proposes the current name, and elaborates on its neoplastic nature

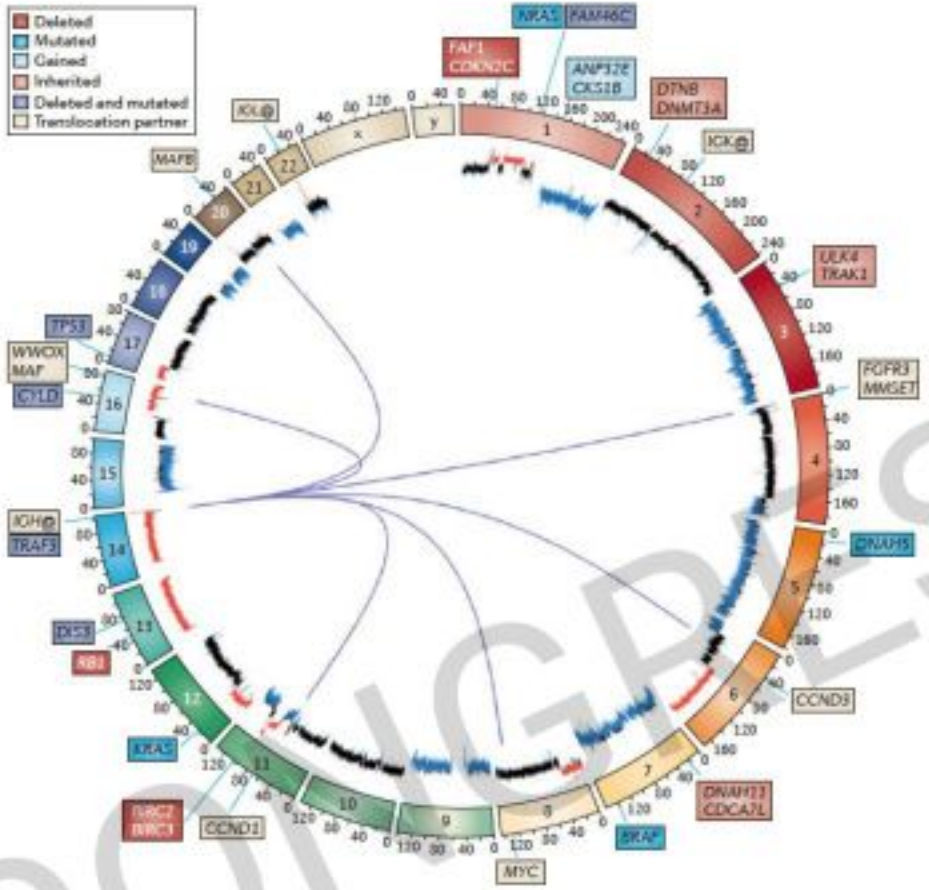
J. von Rustizky. ***Multiples Myelom.*** *Deutsche Zeitschrift fur Chirurgie* (Berlin) 1873; 3: 162-172.

Initiation and Evolution of Multiple Myeloma



Morgan GJ, *Nat Rev Cancer*, 2012

Invariable skeletal involvement



The skeleton is constantly involved despite remarkable genetic and biologic heterogeneity.

- Bone marrow is the prime site of origin
- Metastasis-like spreading throughout the skeleton
- Exquisite *symbiotic* addiction to the bone marrow environment
- Bone involvement is the most prominent clinical aspect ("Myeloma Bone Disease")

Morgan GJ, *Nat Rev Cancer* 2012

Myeloma Bone Disease

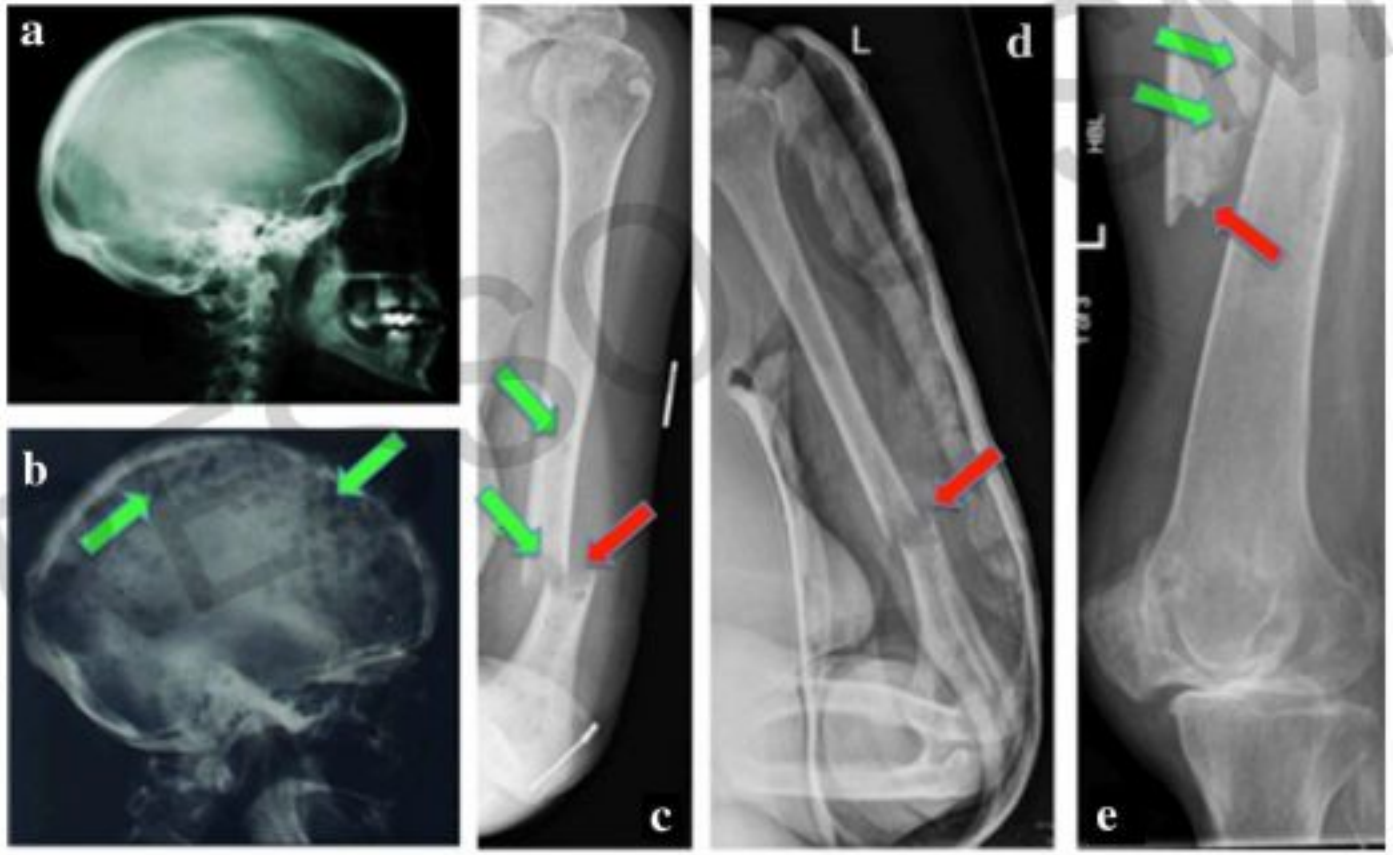


Fig. 1 X-ray examples of serious but preventable myeloma-induced osteolytic lesions and pathological fractures potentially preventable if detected earlier. **a** Normal skull. **b** Myeloma 'pepper pot skull' riddles with lytic lesions. **c**, **d** Pathological fractures through lytic lesions in the distal shaft of the left humerus. **e** Pathological fracture through the proximal shaft of the left femur

Ring ES et al., *Calcif Tissue Int* 2018

Myeloma Bone Disease

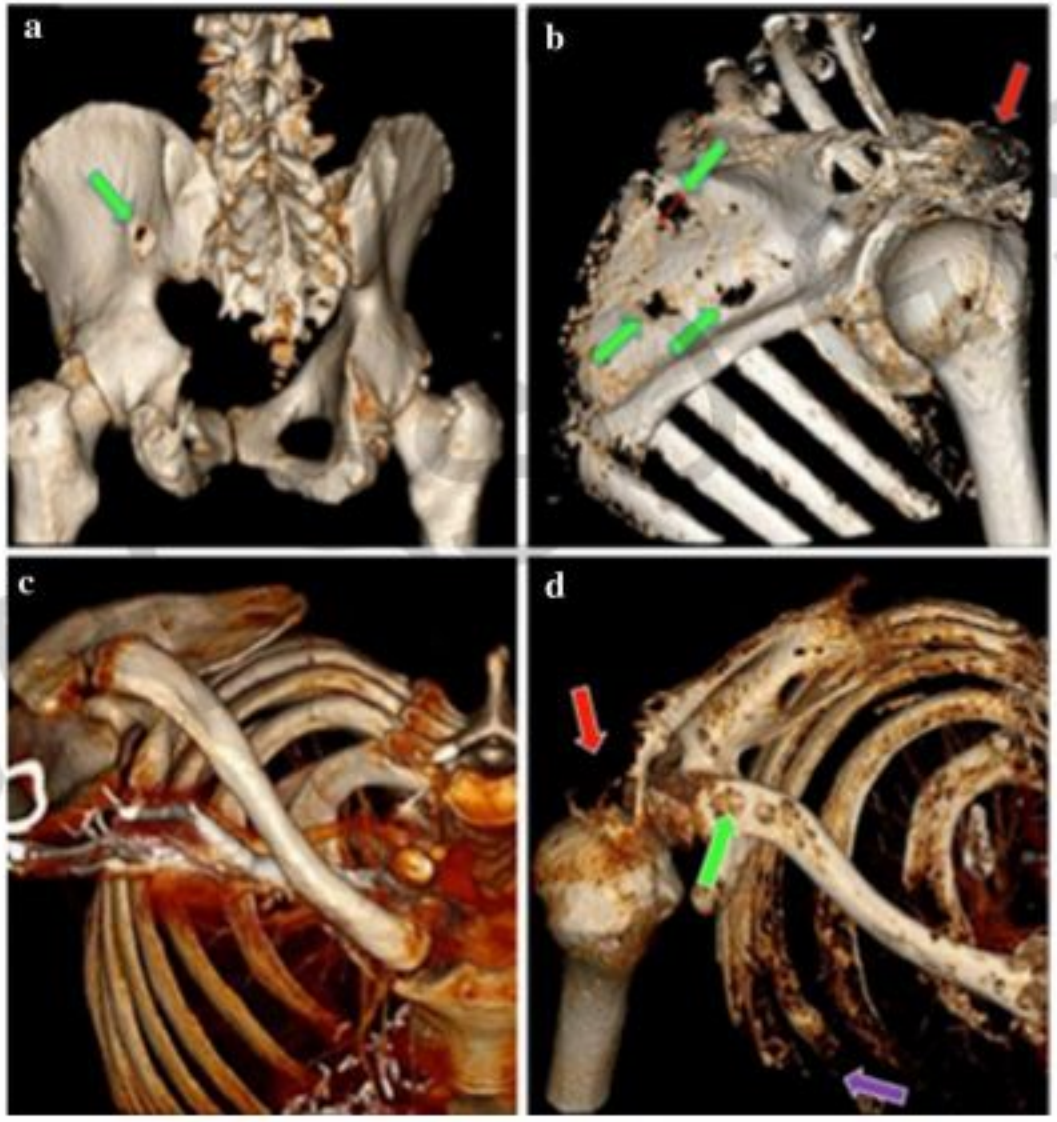


Fig. 2 3D reconstructions of computerised tomography (CT) images using standard diagnostic settings demonstrating two patients with widespread myeloma-induced bone disease, leading to potential serious consequences. **a** Lytic lesion penetrating through the ischium (green arrow). **b** Multiple lytic lesions throughout the scapula (green arrows) with the acromion completely destroyed by myeloma bone disease (red arrow). **c** Example of normal bone from the shoulder, clavicle and ribs. **d** Contrast image of the patient riddled with lytic lesions due to myeloma bone disease. The acromion process is destroyed (red arrow), multiple lytic lesions are present throughout the clavicle (green arrow) and the anterior ribs have been destroyed (purple arrow) (Color figure online)

Ring ES et al., *Calcif Tissue Int* 2018

Increased fracture risk in MGUS

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 19, Number 1, 2004
Published online on December 15, 2003; doi: 10.1359/JBMR.0301212

Fracture Risk in Monoclonal Gammopathy of Undetermined Significance

L JOSEPH MELTON III,[1,2] S VINCENT RAJKUMAR,[3] SUNDEEP KHOSLA,[2] SARA J ACHENBACH,[4] ANN L OBERG,[4] and ROBERT A KYLE[3]

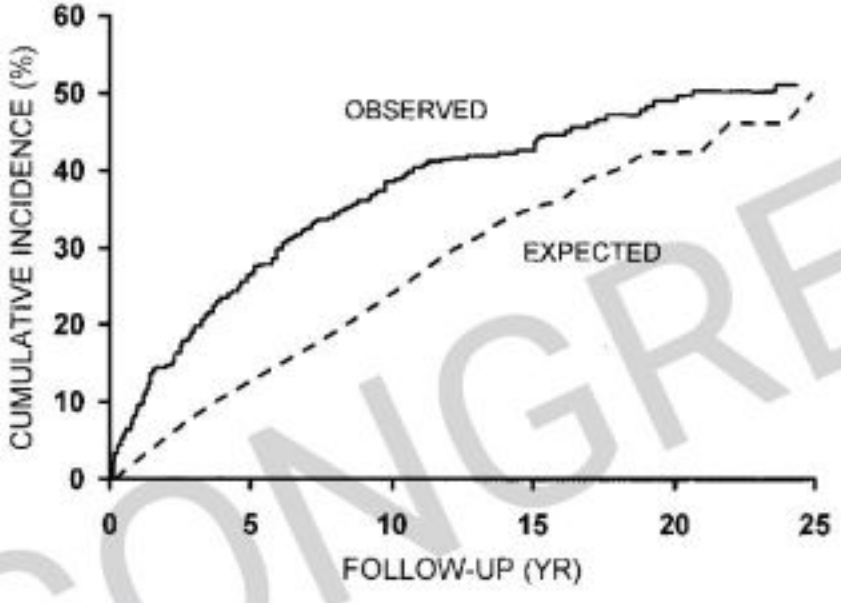


FIG. 1. Observed vs. expected cumulative incidence of fracture ($p < 0.001$) among 488 Olmsted County residents after a diagnosis of MGUS in 1960–1994. Note that death was considered a competing risk in this analysis.

Observed *vs.* expected cumulative incidence of fracture after diagnosis of MGUS in 1960–1994 (n= 488, $P < 0.001$)

- Higher overall (1.7-fold) and site-specific (vertebral) fracture risk (6.3-fold)
- Higher prevalence of MGUS in patients with osteoporosis

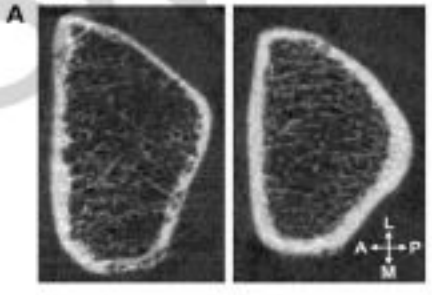
Melton LJ *et al, J Bone Min Res* 2004
Pepe *et al, Br J Haematol* 2006
Gregersen *et al, Br J Haematol* 2006
Golombick *et al, Acta Haematol* 2008
Kristinsson *et al, Blood* 2010
Bida *et al, Mayo Clin Proc* 2009
Edwards *et al, Osteoporosis Int* 2008
Drake *et al, Curr Osteoporos Rep* 2013

Altered bone structure in MGUS individuals

BLOOD, 15 DECEMBER 2011 • VOLUME 118, NUMBER 25

Bone microstructural changes revealed by high-resolution peripheral quantitative computed tomography imaging and elevated DKK1 and MIP-1α levels in patients with MGUS

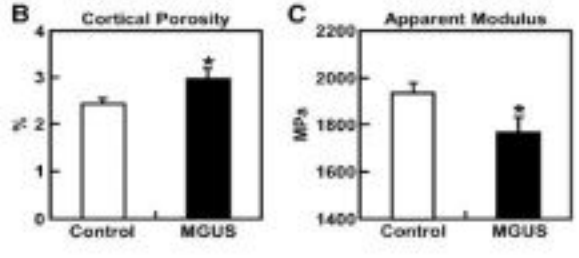
Alvin C. Ng,[1] Sundeep Khosla,[1] Natthinee Charatcharoenwitthaya,[1] Shaji K. Kumar,[2] Sara J. Achenbach,[3] Margaret F. Holets,[1] Louise K. McCready,[1] L. Joseph Melton III,[4] Robert A. Kyle,[2] S. Vincent Rajkumar,[2] and Matthew T. Drake[1]



Altered cortical microarchitecture in patients with monoclonal gammopathy of undetermined significance

Joshua N. Farr,[1] Wei Zhang,[1] Shaji K. Kumar,[1] Richard M. Jacques,[2] Alvin C. Ng,[1] Louise K. McCready,[1] S. Vincent Rajkumar,[1] and Matthew T. Drake[1]

BLOOD, 30 JANUARY 2014 • VOLUME 123, NUMBER 5



HRpQCT in MGUS compared to controls revealed:

- lower total and cortical vBMD, and reduced cortical and trabecular thickness
- higher cortical porosity (+16.8%) and lower strength (–8.9% apparent modulus by μFE analysis)

Monoclonal Gammopathy of ~~Undetermined~~ Skeletal Significance

PERSPECTIVE

JBMR®

Unveiling Skeletal Fragility in Patients Diagnosed With MGUS: No Longer a Condition of Undetermined Significance?

Matthew T Drake

Division of Endocrinology, Metabolism, Nutrition and Diabetes, Department of Medicine, Mayo Clinic, Rochester, MN, USA

Old name:

MGUS, monoclonal gammopathy of **undetermined** significance

(Kyle RA, *Am J Med* 1978)

↓

New name:

MGSS: monoclonal gammopathy of **skeletal** significance

(Drake MT, *J Bone Min Res* 2014)

In view of the long life expectancy of MGUS individuals (75% of which do not progress to MM), strategies are needed to quantify individual fracture risk

Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group

Terpos E, Zamagni E, et al. *Lancet Oncol* 2021

Evangelos Terpos, Elena Zamagni, Suzanne Lentzsch, Matthew T Drake, Ramón García-Sanz, Niels Abildgaard, Ioannis Ntanasis-Stathopoulos, Fredrik Schjesvold, Javier de la Rubia, Charalampia Kyriakou, Jens Hillengass, Sonja Zweegman, Michele Cavo, Philippe Moreau, Jesus San-Miguel, Meletios A Dimopoulos, Nikhil Munshi, Brian G M Durie, Noopur Raje, on behalf of the Bone Working Group of the International Myeloma Working Group

Panel: Updated recommendations for the treatment of myeloma-related bone disease

Patient population

Patients with newly diagnosed myeloma.
Patients with relapsed or refractory myeloma.

Choice

First option

Zoledronic acid (regardless of the presence of myeloma-related bone disease on imaging) for patients with newly diagnosed multiple myeloma or relapsed or refractory myeloma; also consider for patients at biochemical relapse.
Denosumab (only in the presence of myeloma-related bone disease on imaging; also consider for patients with renal impairment).

Second option

Pamidronic acid (when first-option agents are not available or contraindicated).

Administration

Zoledronic acid and pamidronic acid: intravenously.
Denosumab: subcutaneously.

Duration and frequency

Zoledronic acid

Monthly during initial therapy and in patients with less than very good partial response.
If patients achieve a very good partial response or better after receiving monthly administration for at least 12 months, the treating physician can consider decreasing the frequency of dosing to every 3 months or, on the basis of osteoporosis recommendations, to every 6 months or yearly, or discontinuing zoledronic acid.
If discontinued, it should be reinitiated at the time of biochemical relapse to reduce the risk of new bone event at clinical relapse.

Denosumab

Continuously, monthly.
If discontinued, a single dose of zoledronic acid should be given to prevent rebound effects at least 6 months after the last dose of denosumab; also consider giving denosumab every 6 months.

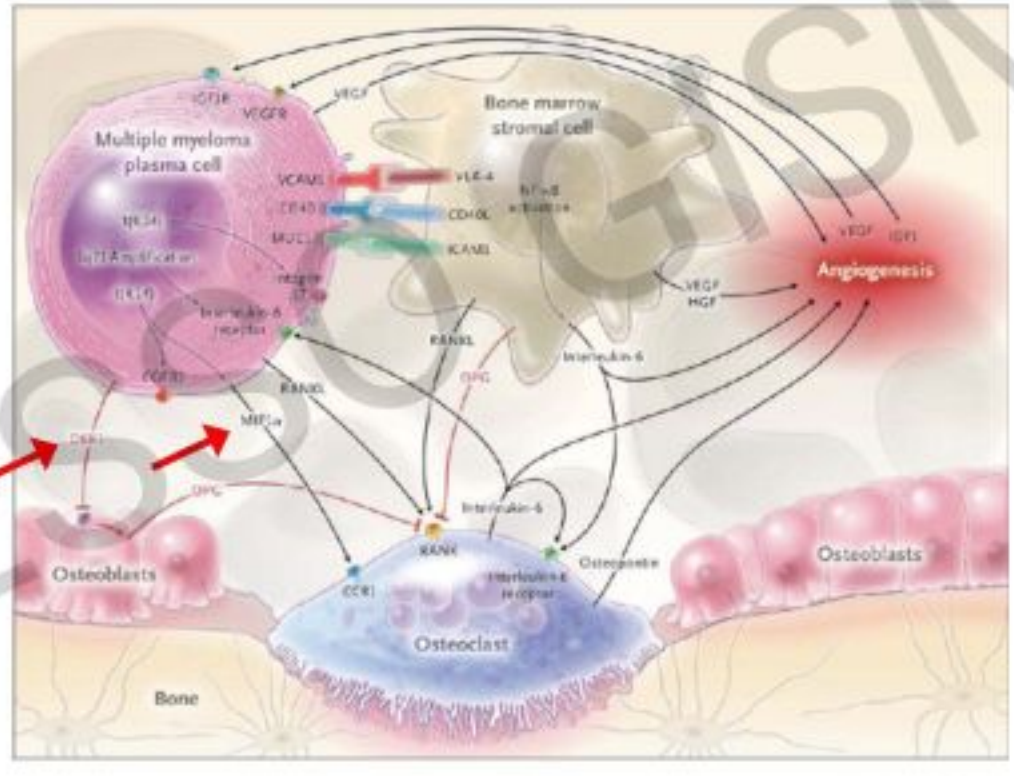
Monitoring and preventive measures

Creatinine clearance and serum electrolytes (monthly) for zoledronic acid, plus urinary albumin (monthly) for pamidronic acid; these tests are not needed for denosumab.
Dental health (at baseline, then at least annually or if symptoms appear) for both bisphosphonates and denosumab.
Calcium and vitamin D supplementation is recommended for all patients for both bisphosphonates and denosumab.
Patient education for early recognition and reporting of adverse events for both bisphosphonates and denosumab.

Any new therapeutic opportunities?

How does myeloma disrupt bone remodeling?

Multiple cell types
(**plasma cells, BM stromal cells, osteoblasts, osteocytes, osteoclasts**)
and multiple ligands
(**cytokines, Wnt inhibitors**)
act multi-directionally to suppress osteoblast differentiation and bone formation, and to promote osteoclast activity ***(uncoupling)***



Palumbo and Anderson, *NEJM* 2011
Teramachi J et al, *Leukemia* 2016

Increased DKK1 (2x) and MIP-1alpha (6x) in MGUS

Roussou et al, *Leukemia* 2009
Ng *et al*, *Blood* 2011

High sclerostin in multiple myeloma

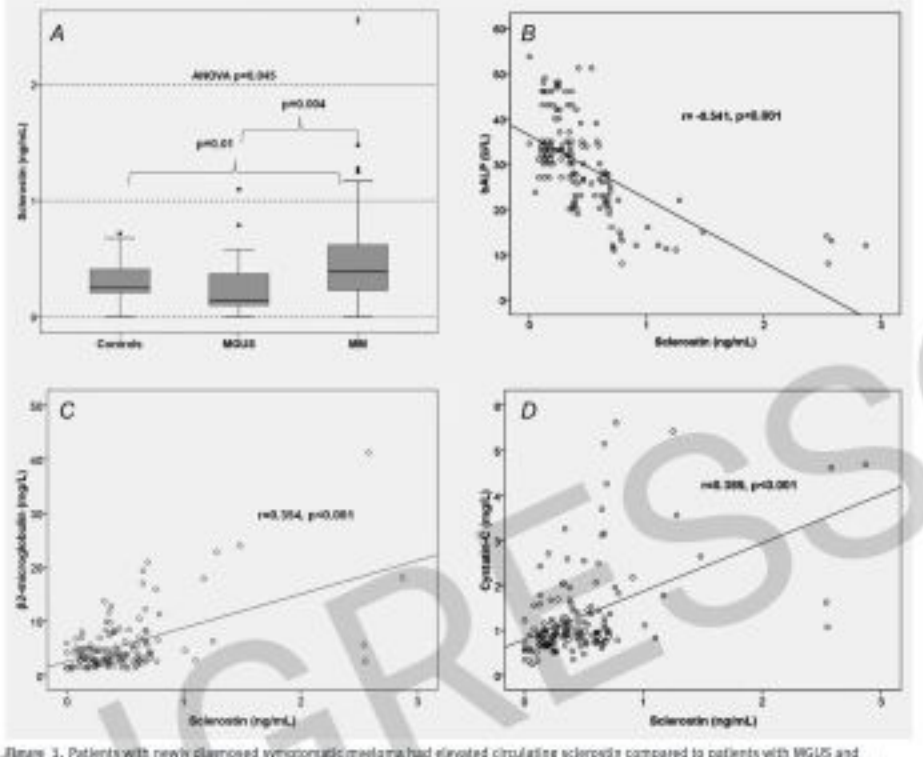


Figure 1. Patients with newly diagnosed symptomatic myeloma had elevated circulating sclerostin compared to patients with MGUS and healthy controls (1A; see also Tables 1 and 2). Circulating sclerostin correlated with bALP (1B), beta2-microglobulin (1C), and cystatin C (1D).

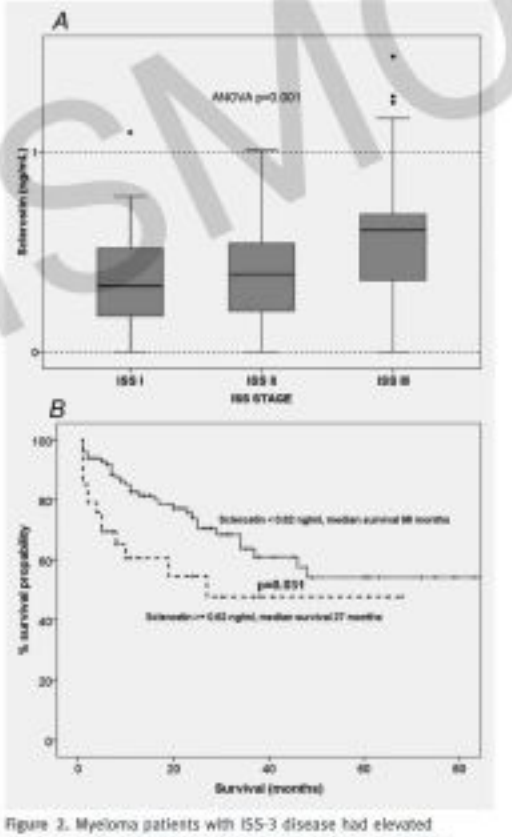


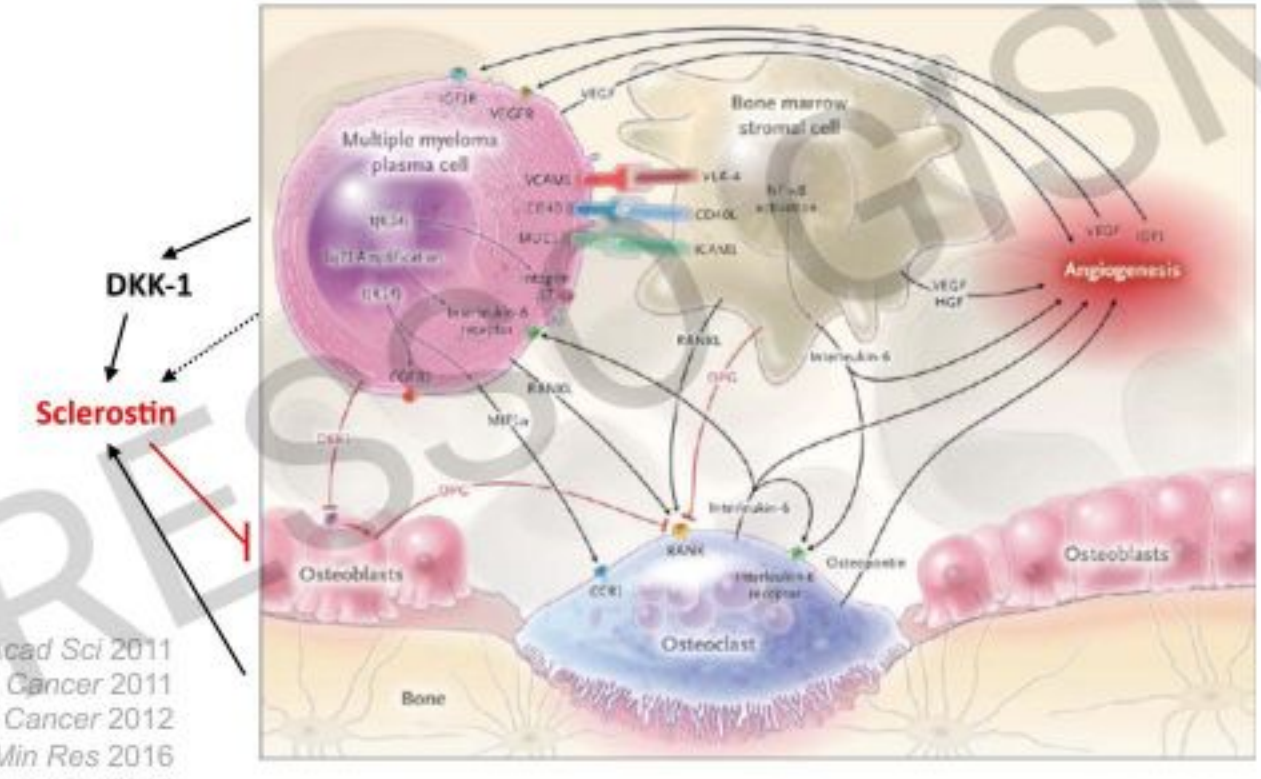
Figure 2. Myeloma patients with ISS-3 disease had elevated circulating sclerostin compared to patients with ISS-1 ans ISS-2 disease (2A). Patients who had a serum sclerostin of ≥0.62 ng/ml (upper quartile, n = 40 patients) had a median survival of 27 months, while the median survival of all other patients was 98 months (2B).

- Sclerostin increased in MM patient serum and bone marrow
- Elevated sclerostin correlates with poor overall survival

Brunetti G et al, *Ann N Y Acad Sci* 2011
Wang X-T et al, *Leuk Res* 2014
Loredana S, *J Bone Min Res* 2016
Terpos E, *Int J Cancer* 2011

How does myeloma disrupt bone remodeling?

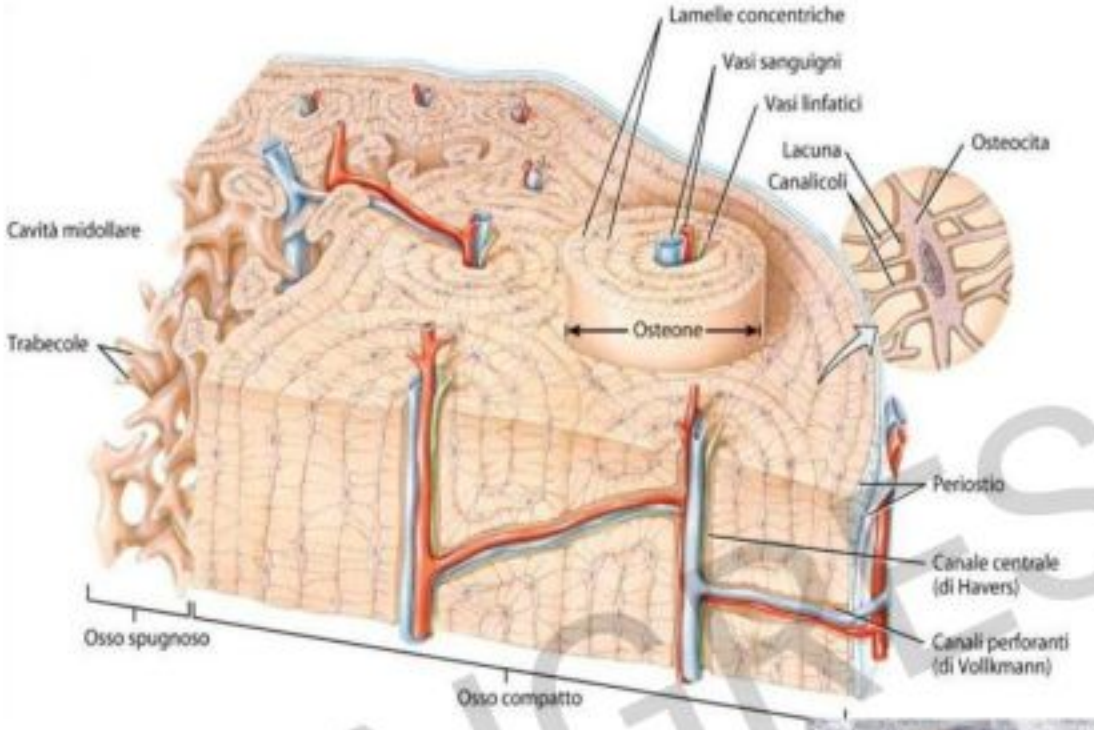
Increased production of the Wnt antagonist **sclerostin** by **osteocytes** (and tumor cells) suppresses osteoblast maturation and bone formation



Brunetti G et al, *Ann N Y Acad Sci* 2011
Colucci S et al, *Blood Cancer* 2011
Tarpos E et al, *Int J Cancer* 2012
Eda H et al, *J Bone Min Res* 2016
Delgado-Calle J et al, *Leukemia* 2017

Palumbo and Anderson, *NEJM* 2011
Teramachi J et al, *Leukemia* 2016

Osteocytes

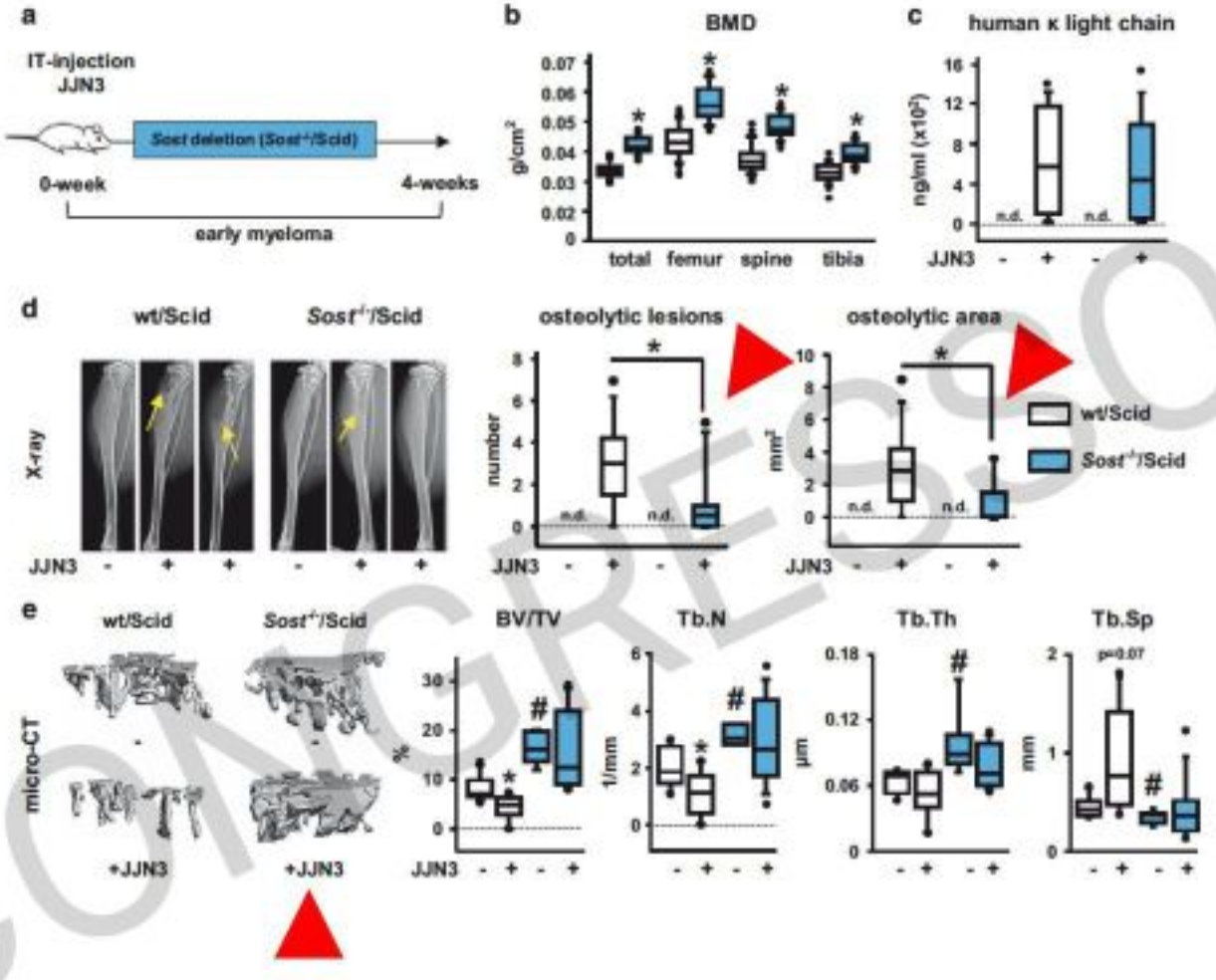


- The most abundant cellular population in bone (**42x10^{9}** cells)
- Originate from osteoblasts that remain embedded in the matrix they deposited
- Interconnected in a vast **network** (**23x10^{12}** connections)*
- Reside in an extended canalicular system: **74 km/cm^{3}**
- **>200 m^{2}** bone surface interfaces the osteocyte network

(*) …*this* is a real neural network…!

Sims NA & Martin TJ. *Front Endocrinol.* **2015**; 6(41):1-5
Dallas SL et al. *Endocr Rev.* **2013**; 34, 658–690
Kollmannsberger P et al. *New J. Phys.* **2017**; 19, 073019
Buenzli PR & Sims NA. *Bone* **2015**; 75, 144–150
Schaffler MB et al. *Calcif Tissue Int.* **2014**; 94, 5–24

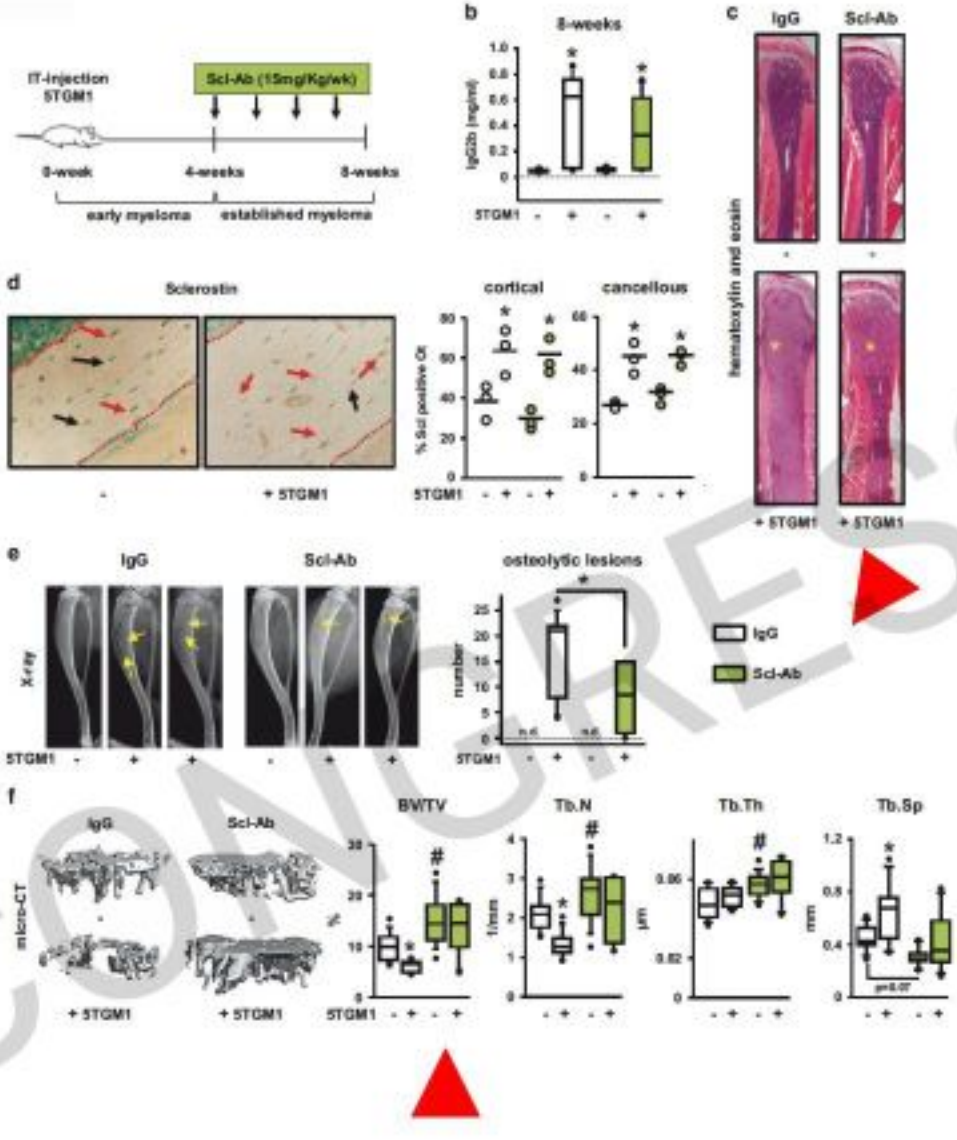
Sclerostin in Myeloma Bone Disease (I)



Myeloma bone disease is prevented in sclerostin-null mice

Delgado-Calle J *et al*, *Leukemia* 2017

Sclerostin in Myeloma Bone Disease (II)



Treatment with Scl-Ab reduces the number of osteolytic lesions and prevents the loss of trabecular bone in an immunocompetent mouse model of MM.

Delgado-Calle J *et al*, *Leukemia* 2017

Sclerostin in Myeloma Bone Disease (III)

Regular Article

blood

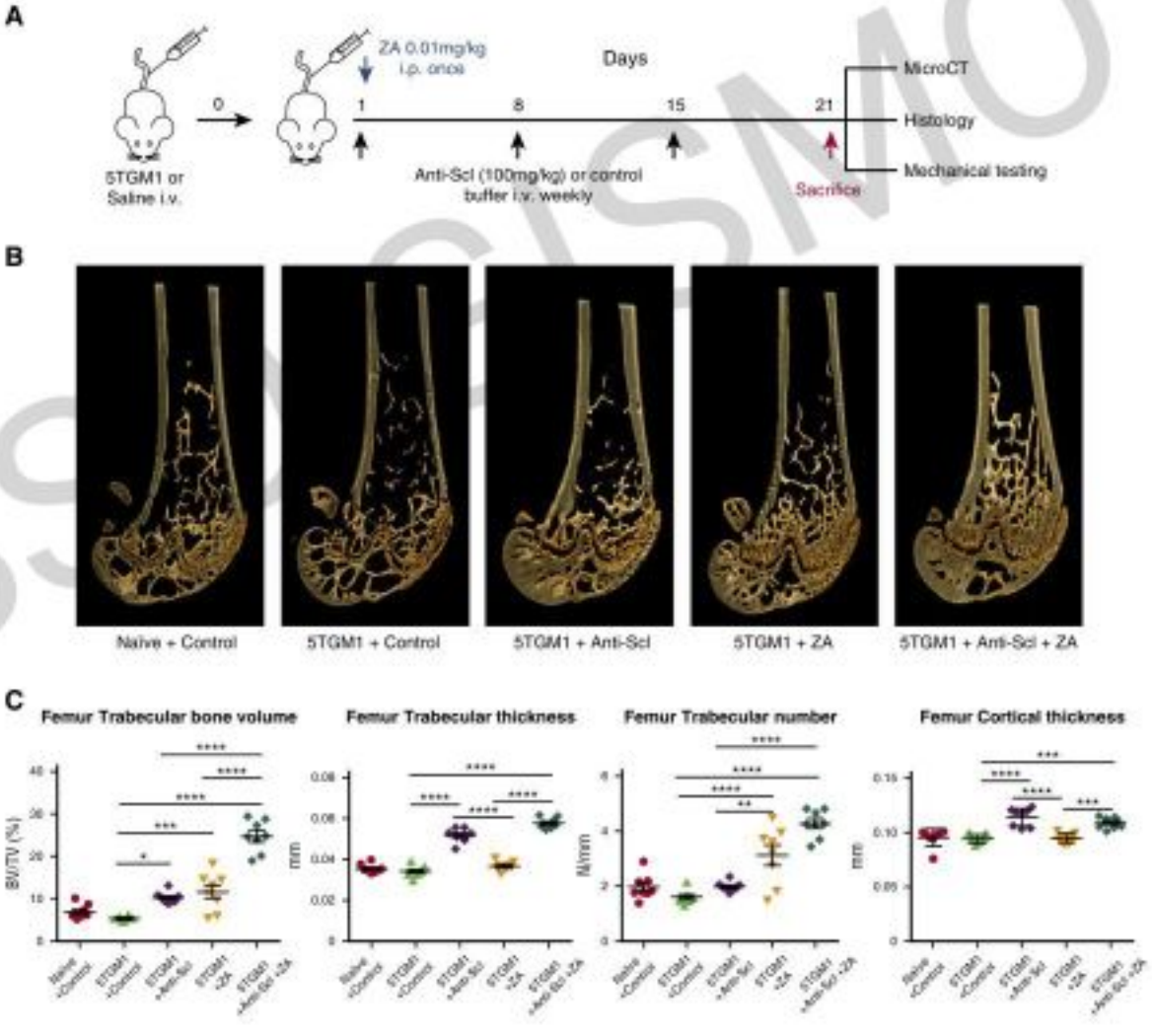
LYMPHOID NEOPLASIA

Inhibiting the osteocyte-specific protein sclerostin increases bone mass and fracture resistance in multiple myeloma

Michelle M. McDonald,[1,2] Michaela R. Reagan,[3,4] Scott E. Youlten,[1,2] Sindhu T. Mohanty,[1] Anja Seckinger,[5] Rachael L. Terry,[1,2] Jessica A. Pettitt,[1] Marija K. Simic,[1] Tegan L. Cheng,[6] Alyson Morse,[6] Lawrence M. T. Le,[1] David Abi-Hanna,[1,2] Ina Kramer,[7] Carolyne Falank,[4] Heather Fairfield,[4] Irene M. Ghobrial,[3] Paul A. Baldock,[1,2] David G. Little,[8] Michaela Kneissel,[7] Karin Vanderkerken,[5] J. H. Duncan Bassett,[9] Graham R. Williams,[9] Babatunde O. Oyajobi,[10] Dirk Hose,[5] Tri G. Phan,[1,2] and Peter I. Croucher[1,2]

Key Points

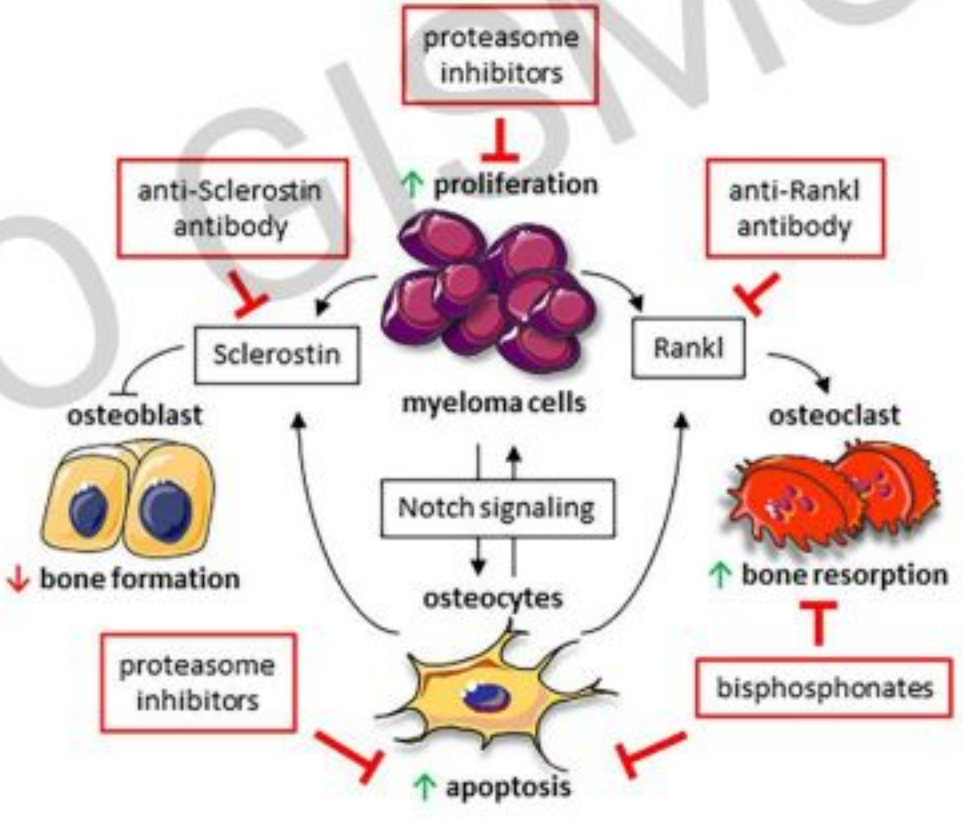
- Anti-sclerostin treatment increases bone mass and fracture resistance in MM
- Anti-sclerostin in combination with zoledronic acid is superior to zoledronic acid alone in increasing fracture resistance.



McDonald MM *et al*, *Blood* 2017

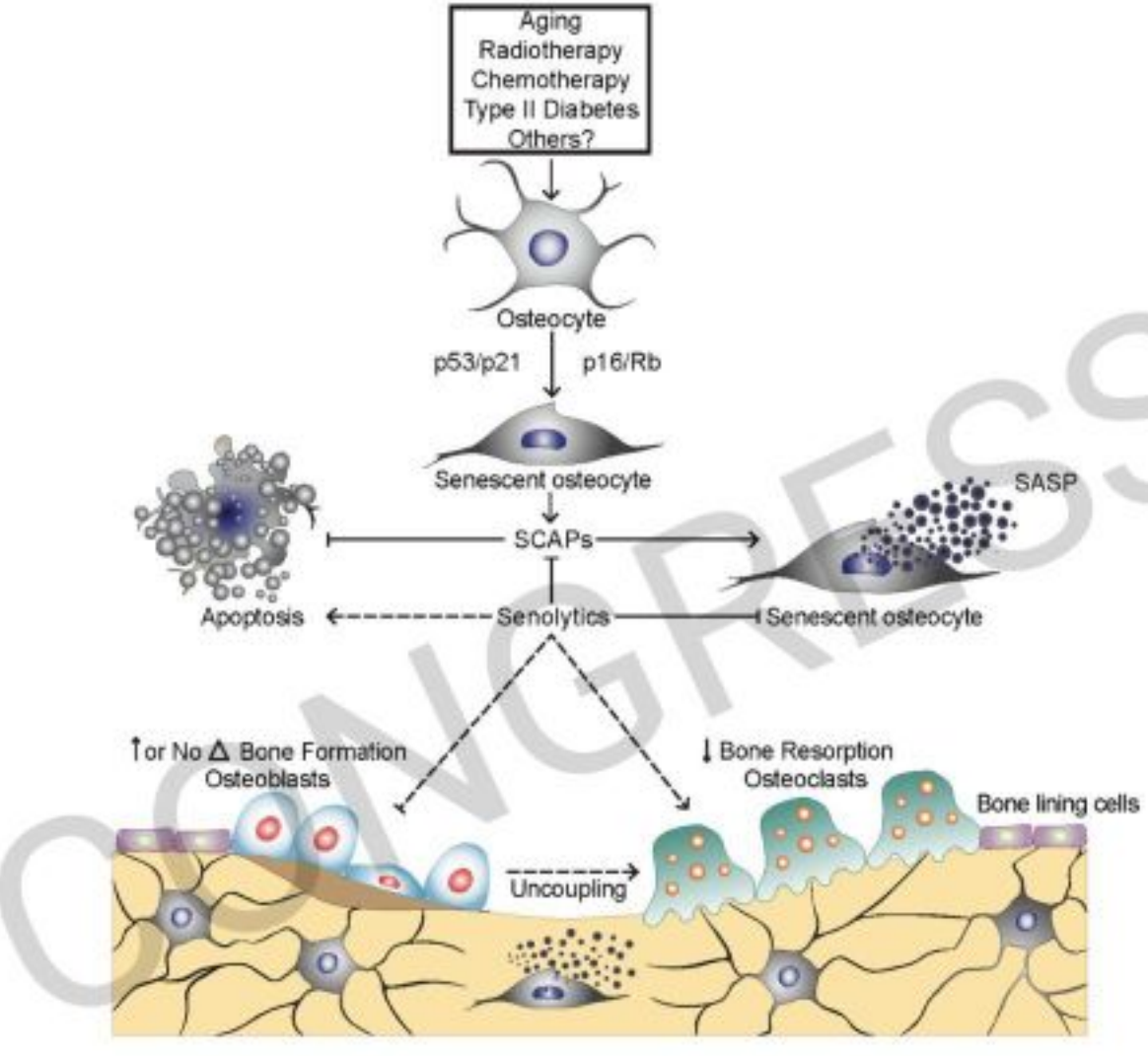
MBD therapy beyond SRE prevention

- **Growing need** to **prevent myeloma SREs** (skeletal-related events), as survival increases
- Anti-MBD agents **zoledronate** and **anti-RANKL mAb** **increase overall survival**
- Benefits may extend beyond bone disease owing to **direct anti-myeloma effects** (ex, zoledronate) and to **causal role** of bone alterations in **disease progression**
- Other agents hold promise but await validation (ex, **anti-sclerostin mAb**)



Morgan GJ et al, *Lancet* 2010
Raje N et al, *Lancet Oncol.* 2018
Terpos E et al, *Blood Cancer J.* 2018
Atkinson EG & Delgado-Calle J, *JBMR Plus* 2019

(Keep an eye on senolytics)



Targeting osteocyte senescence may offer a valuable therapy against not only **aging**-associated, but also **radio/chemotherapy**-, **T2DM**- and **cancer**-associated bone damage, possibly extending to virtually **all bone wasting conditions**.

Farr JN et al, *Curr Osteop Rep* 2020

Grazie