R.S.LORENC

ECHA ASBMR, DENVER 2017

ŁÓDZ,13-TY STYCZNIA 2018

TEZY:
40 –LECIE ASBMR, WSPÓŁDZIAŁANIE KOŚCI Z INNYMI NARZĄDAMI, MARKERY METABOLICZNE, STARZENIE SIĘ , PODSUMOWANIE

JBMR®

Reflecting on Some Discoveries of 40 Years and Their Outcomes

It is a privilege to reflect upon the impact of advances in basic/translational research in the field over the last 40 years. My approach has been to take a single theme and provide a historical account of notable advances over that time and what impact they might have. The theme of intercellular communication in bone remained of interest to me throughout that time: the main discoveries and how they were made, the major changes in thinking, and how they have influenced concepts of bone remodeling. When I came to bone research more than 40 years ago, and for quite some years after that, essentially no regulatory influences were considered except circulating hormones. Endocrinology subsequently gave way to paracrinology, with discoveries of local events providing ways to think about bone remodeling, which is so central to all approaches to the prevention and treatment of diseases involving bone loss.

Proposing the Remodeling Concept

Any view of modern concepts of bone remodeling began with Harold Frost in the 1960s[1]: based on cortical bone in human and dog rib, he proposed that a process he described as "coupling" took place, by which resorption by osteoclasts at a particular site was followed by formation of an equal amount of bone formation. He wrote much about it over the next years, as did Michael Parfitt,[2,3] promoting the concept that remodeling of bone took place in packets asynchronously throughout the skeleton. Frost referred to those packets as basic multicellular units (BMUs), which became the preferred terminology. The realization that there was a quiescent interval after resorption and before the onset of formation led Roland Baron in the early 1970s to consider this interval and call it the "reversal phase" of remodeling, and to suggest that it might be an important stage in the remodeling process.[4] Although they were prescient writings, little attention was paid to the reversal phase over the next almost 30 years, but it is now the focus of new and deserved attention.

Cells of Bone Communicate With Each Other: Osteoblastic Cells Regulating Osteoclasts

Cells were extracted from 3-week-old rodent bone by collagenase digestion in Bill Peck's laboratory in 1964; cells that were alkaline phosphatase–positive and underwent aerobic metabolism of glucose, but could not be studied long-term.[5] Only in the late 1970s could bone cells be studied in culture for the first time, when they were obtained from the development of rodent osteosarcomata able to make a bone-like ground substance and mineralize it in vivo,[6] from which cells could be grown with many properties that might have been expected of osteoblasts.[7,8] Importantly, at the same time, David Cohn's group prepared cells from newborn rodent bone by sequential enzymatic digestion, yielding cultures enriched in osteoblasts.[9] Both osteosarcoma and the calvarial cells were exquisitely parathyroid hormone (PTH)–responsive and rapidly became useful in studying hormone action.[10,11] One feature was the relative responsiveness in these cells to PTH peptides and to prostaglandins, their metabolites, and analogs. These dose-responsive patterns were evident in promoting cyclic AMP production in very short-term assays of only a few minutes.[12] Virtually exactly the same relative efficacies were obtained in promoting bone resorption in organ cultures—usually 48-hour cultures ending in increased osteoclasts.[13]

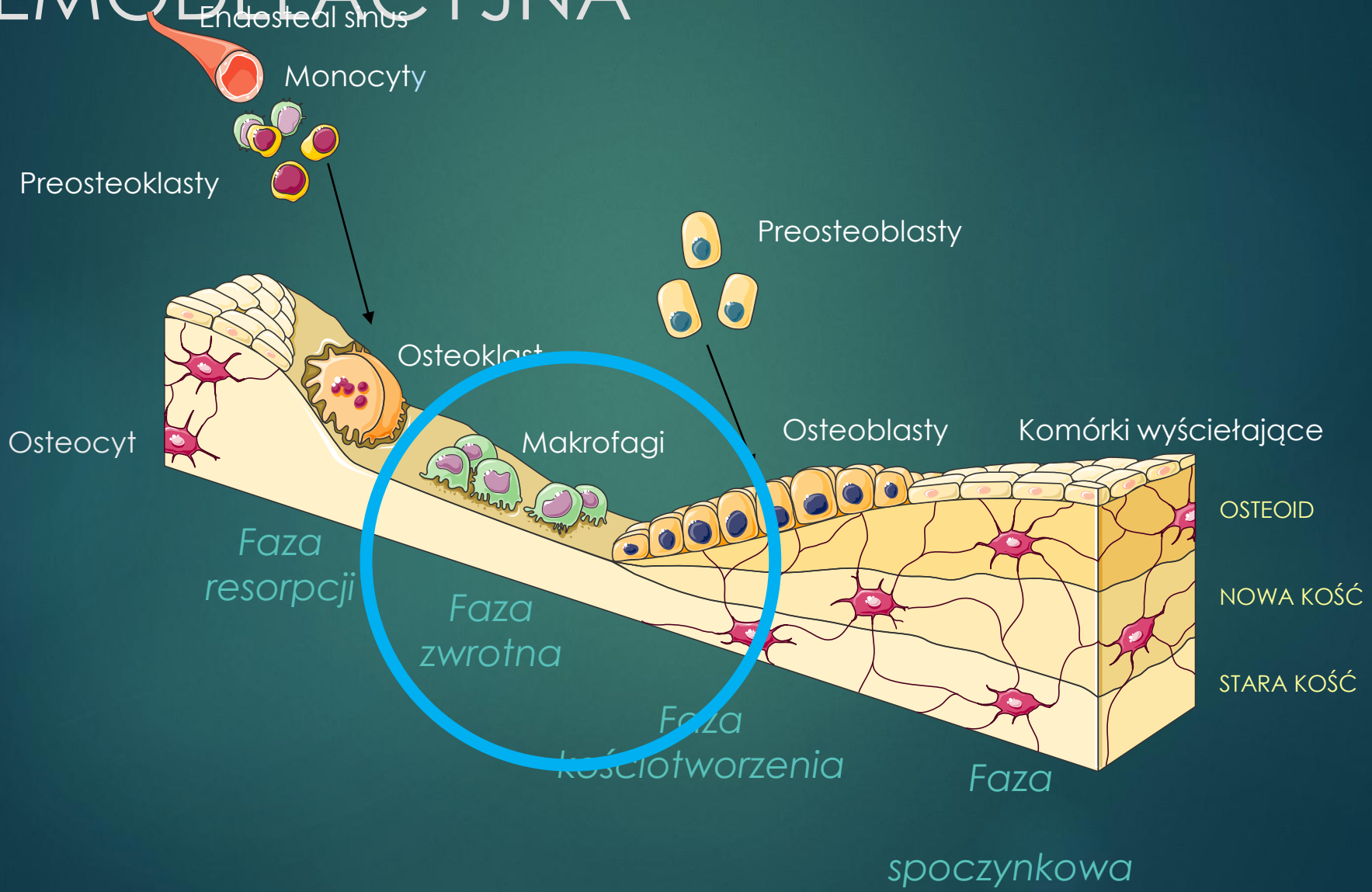
The latter bone resorption findings came first from the laboratories of Larry Raisz and Armen Tashjian in the 1970s, when investigating mechanisms of increased bone resorption in cancer.[14,15] These assay outcomes, together with the findings of SJ Jones and Alan Boyde[16] that bone lining cells retracted on the surface in response to PTH and constituted a barrier to osteoclasts reaching the bone surface, led to the hypothesis that resorbing hormones acted upon the osteoblast lineage to breach this barrier and osteoclasts reached mineralized matrix.[13,17] This concept included the view that osteoblast lineage cells generate signals leading to the recruitment, maturation, and activation of osteoclasts.[18]

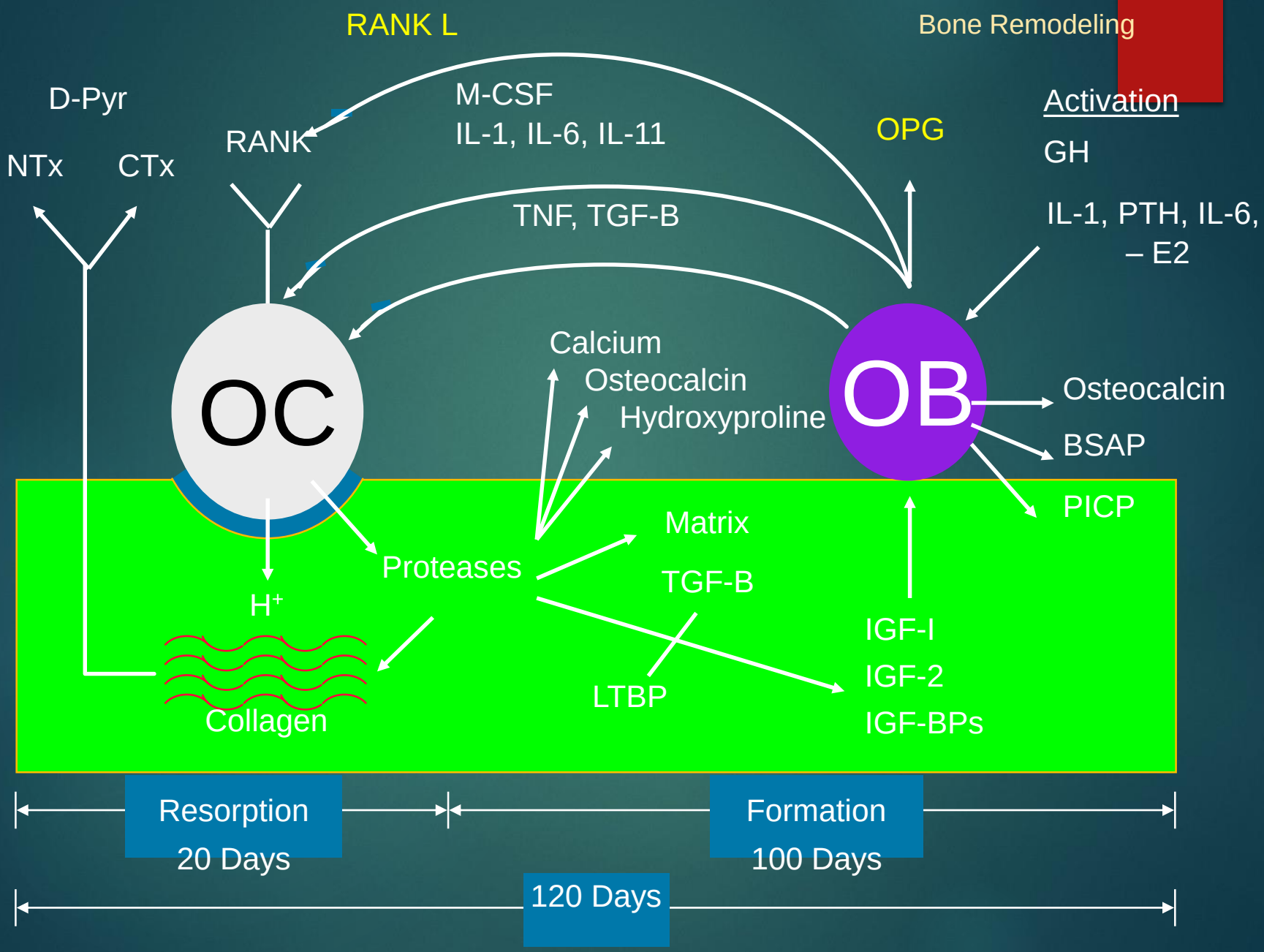
The same hypothesis came from Tim Chambers[19] based on different thinking—that osteoclasts were wandering cells—and it made sense for them to be programmed by genuine bone cells: osteoblasts. In fact, I quote the late Maureen Owen, who had done beautiful work years earlier on the origin of bone cells—particularly osteoblasts: "anyone who has looked at histologic sections of bone will have been struck by the paucity of osteoclasts compared with the number of osteoblasts"[20]—it seemed that osteoclasts only came where and when they were needed, as Chambers argued, and it made no sense for their development to be orchestrated by any circulating factors.

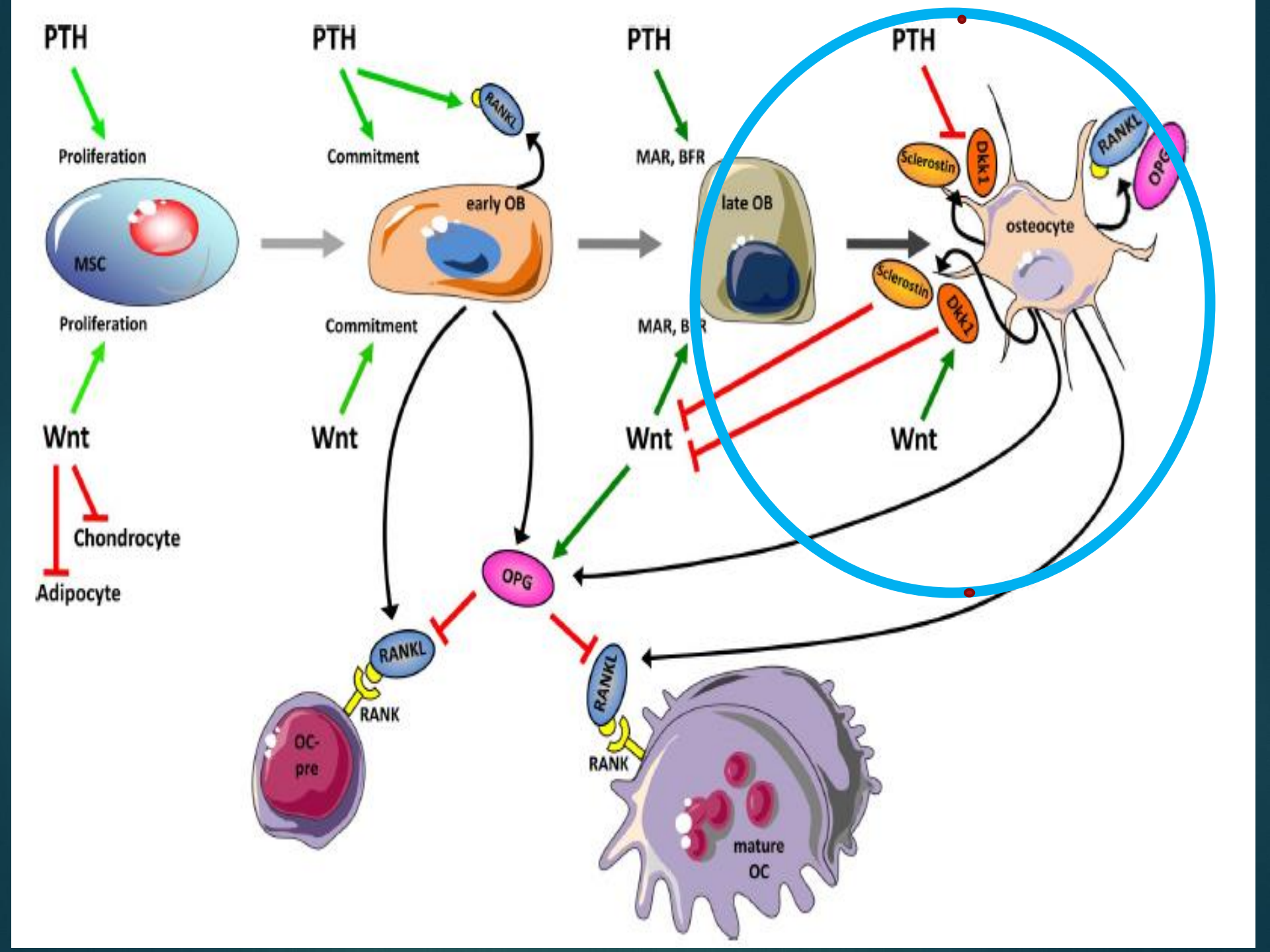
This hypothesis, that osteoclast biology was controlled by osteoblast lineage cells, was influential and it certainly disturbed a lot of people at the time—but it was just a hypothesis, to be proven false if it were so. However, the possibility soon came to be considered as one worth studying, and it rapidly came to feature prominently in abstracts at ASBMR meetings.

Journal of Bone and Mineral Research, Vol. 32, No. 10, October 2017, pp 1971–1976
DOI: 10.1002/jbmr.3282

STRUKTURALNA JEDNOSTKA REMODELACYJNA




RANK L
Bone Remodeling
D-Pyr
NTx
CTx
RANK
M-CSF
IL-1, IL-6, IL-11
OPG
Activation
GH
IL-1, PTH, IL-6,
– E2
TNF, TGF-B
OC
Calcium
Osteocalcin
Hydroxyproline
OB
Osteocalcin
BSAP
PICP
Matrix
TGF-B
Proteases
H+
IGF-I
IGF-2
IGF-BPs
LTBP
Collagen
Resorption
20 Days
Formation
100 Days
120 Days


PTH
Proliferation
MSC
Proliferation
Wnt
Chondrocyte
Adipocyte
PTH
Commitment
RANKL
early OB
Commitment
Wnt
PTH
MAR, BFR
late OB
MAR, B
Wnt
PTH
Sclerostin
Dkk1
osteocyte
RANKL
OPG
Sclerostin
Dkk1
Wnt
OPG
RANKL
RANK
OC-
pre
RANKL
RANK
mature
OC

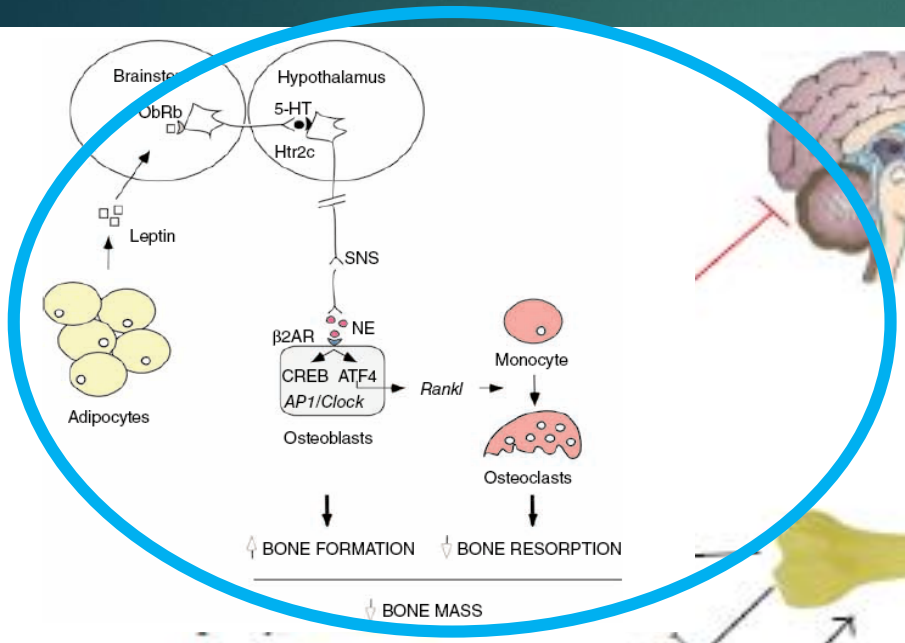
DŁUGOŚĆ ŻYCIA KOMÓREK KOSTNYCH

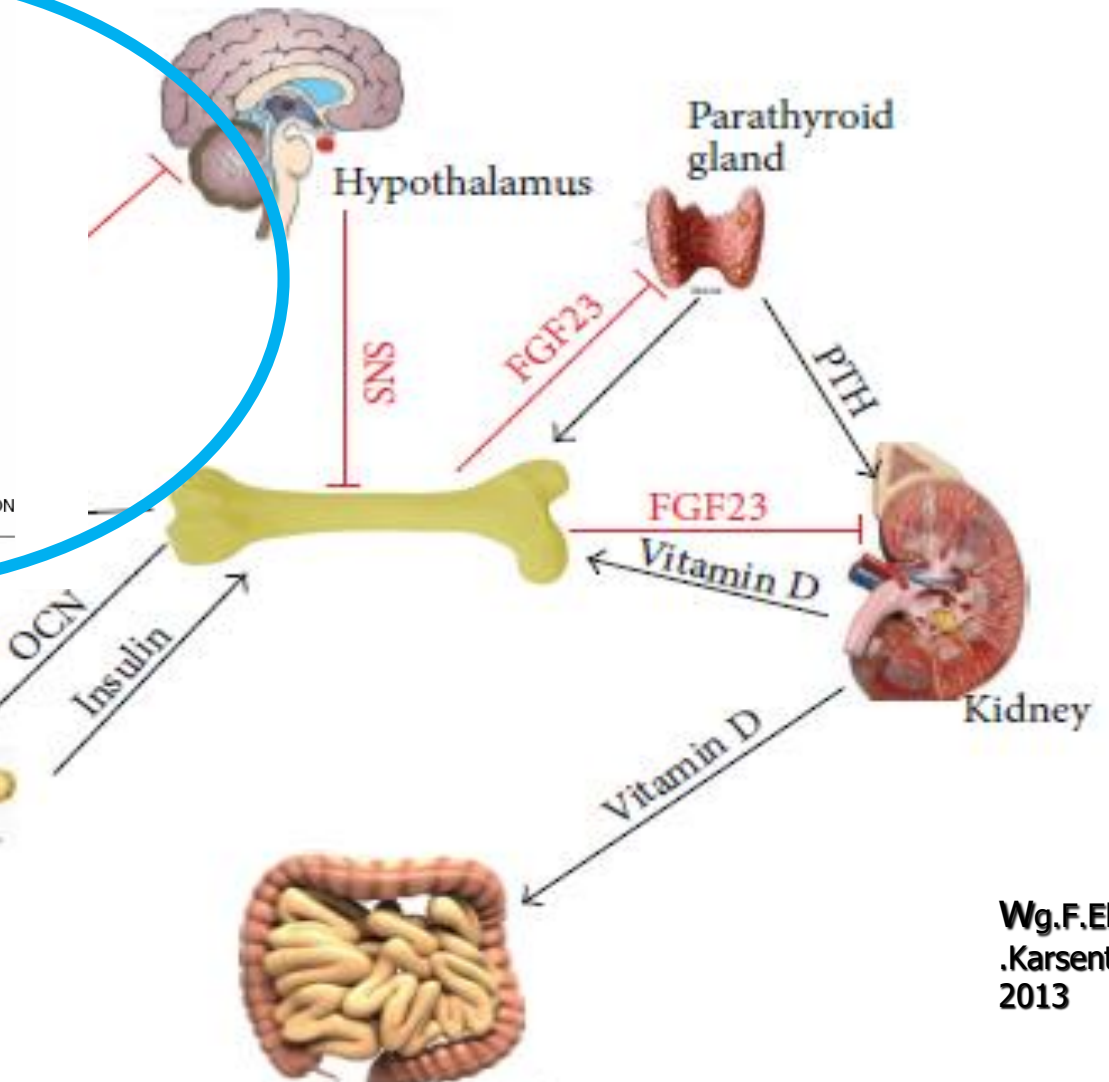
wg.Monolagas i Parfitt 2010

1. Osteoklast 1-25 dni
2. Osteoblast 1-200 dni
3. Komórki pokrywające 1-10 lat
4. Osteocyty 1-50 lat
5. MSC przyżyciowo

TKANKA KOSTNA W METABOLIŻMIE USTROJOWYM:

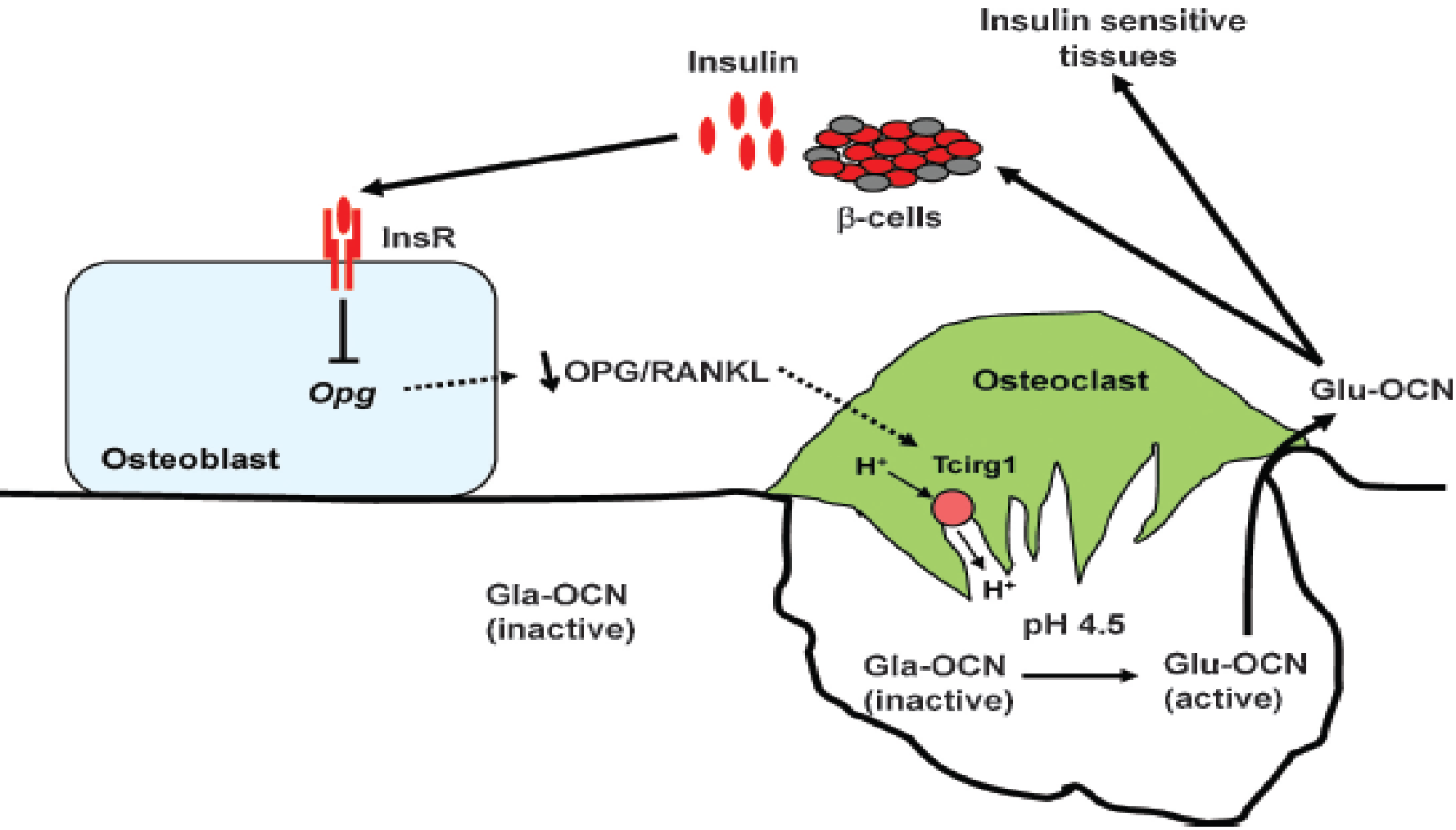
UDZIAŁ TKANKI KOSTNEJ W METABOLIŻMIE USTROJOWYM



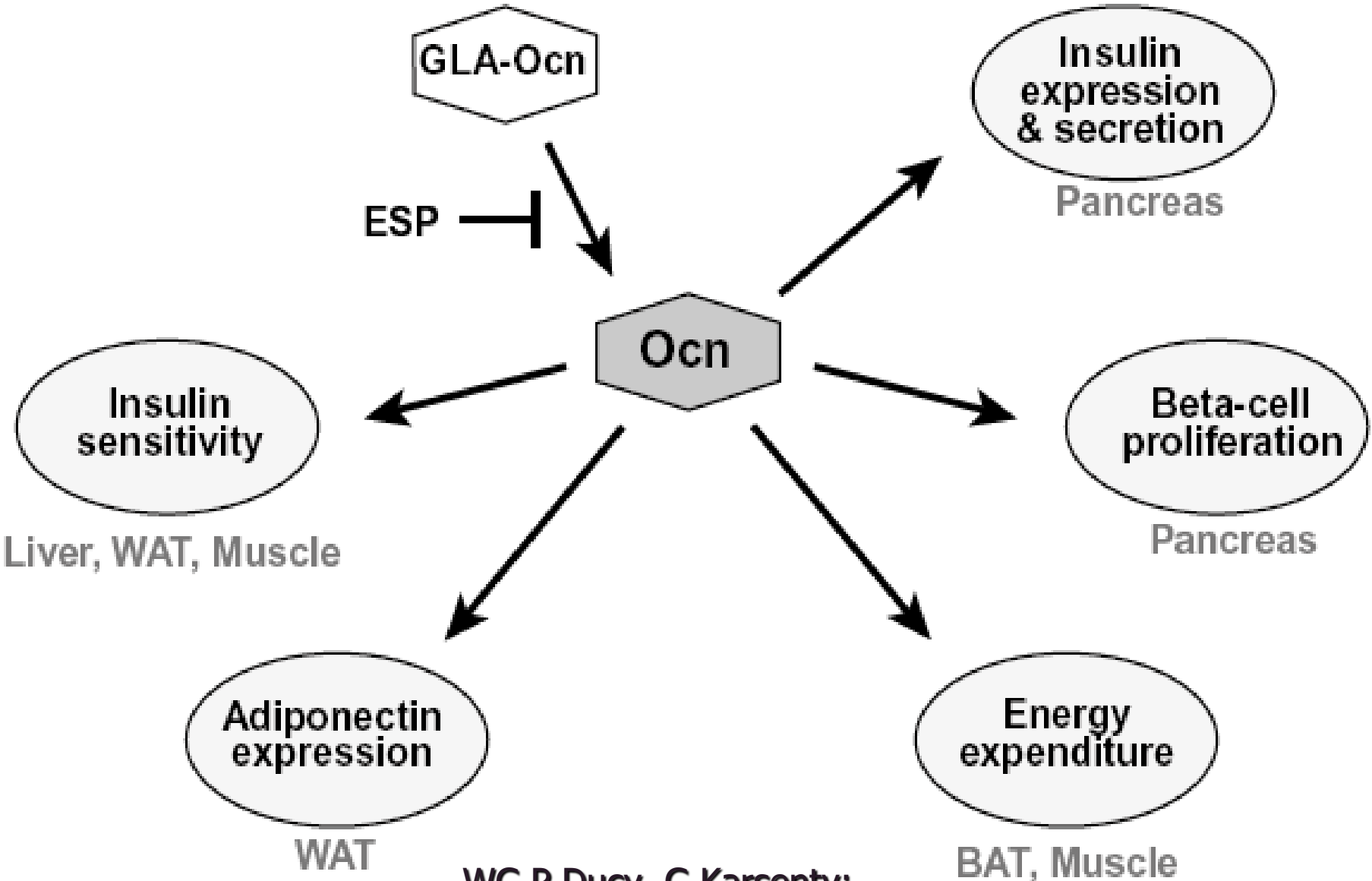


Wg.F.Elefteriou, .Karsenty Primer 2013

WPŁYW INSULINY NA METABOLIZM KOSTNY wg.Ducy and Karsenty2016

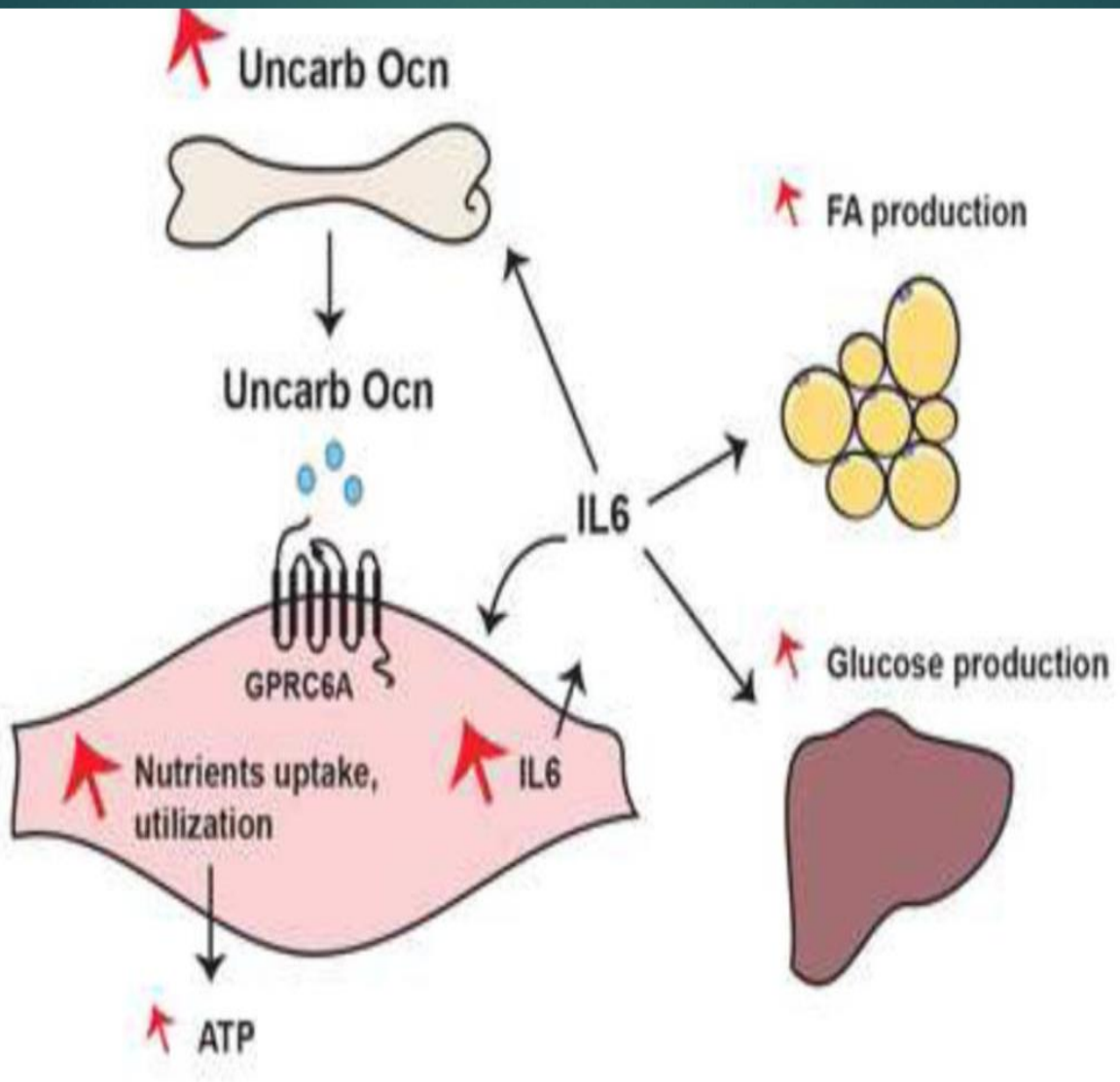


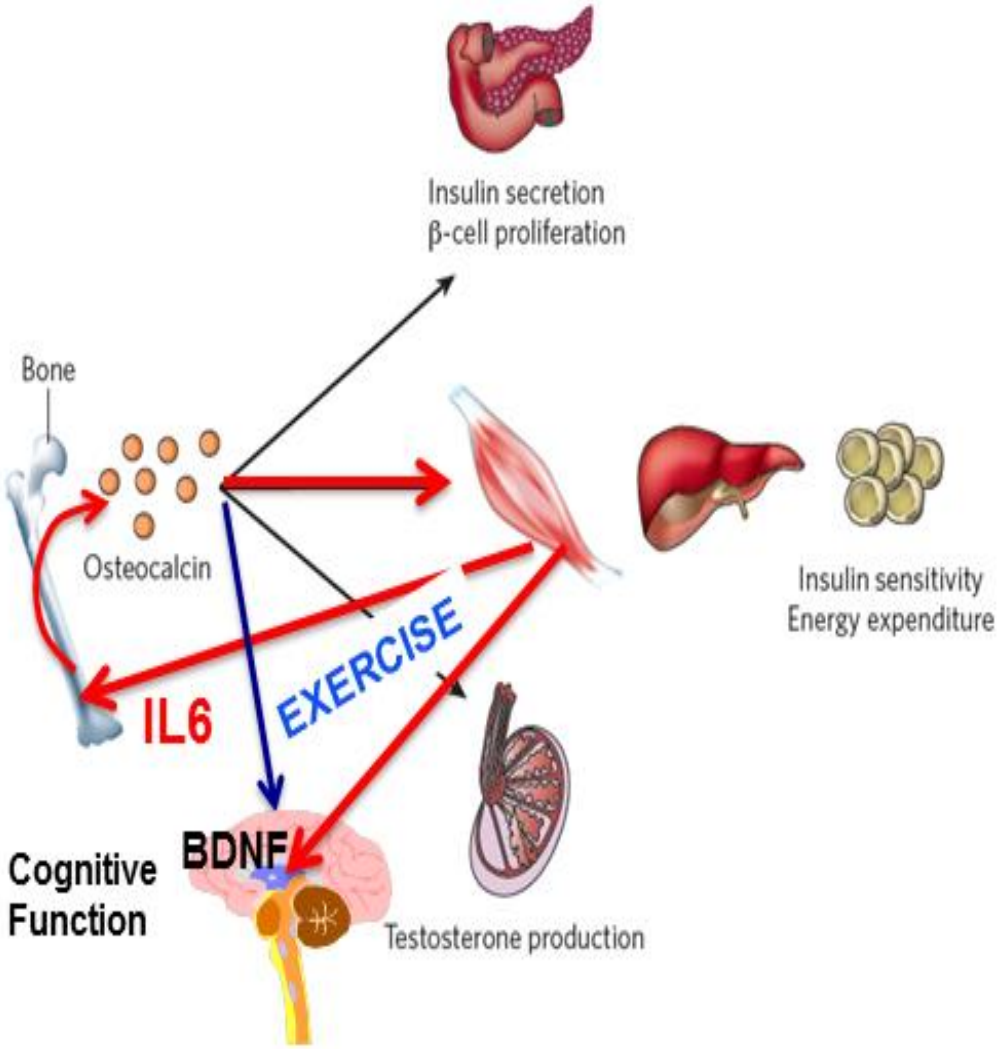
METABOLICZNE FUNKCJE OSTEOKALCYNY



WG.P.Ducy, G.Karsenty; Primer 2013

Osteokalcyna w adaptacji na wysilek fizyczny wg.Karsenty et al 21017





Mera et al. Cell Metab. 2016

Adapted from Karsenty and Ferron. *Nature*. 2012

MARKERY OBROTU KOSTNEGO

PRZYDATNOŚĆ KLINICZNA BTM wg.IOF:

- the **IOF** recommends Bone Markers for therapy monitoring and prediction of fragility fractures

- Bone Markers allow the assessment of the **rate of bone formation or bone loss**. This allows the identification of patients at high risk for bone fractures.

- Bone Marker tests are less expensive than **Bone Mineral Density** (BMD) measurements.

- Bone Markers do not replace BMD but are a **complementary diagnostic tool** as they provide information about the rate of bone loss and not the patient's current BMD.

- **three main clinical applications** can be defined for Bone Markers:

Therapy Monitoring

Adherence Testing

Risk Assessment

STANOWISKO GRUPY ROBOCZEJ IOF

1. Ograniczenie liczby analizowanych markerów BTM
2. Standaryzacja norm i procedur postępowania
3. Automatyzacja oznaczeń

Stanowisko grupy roboczej IOF

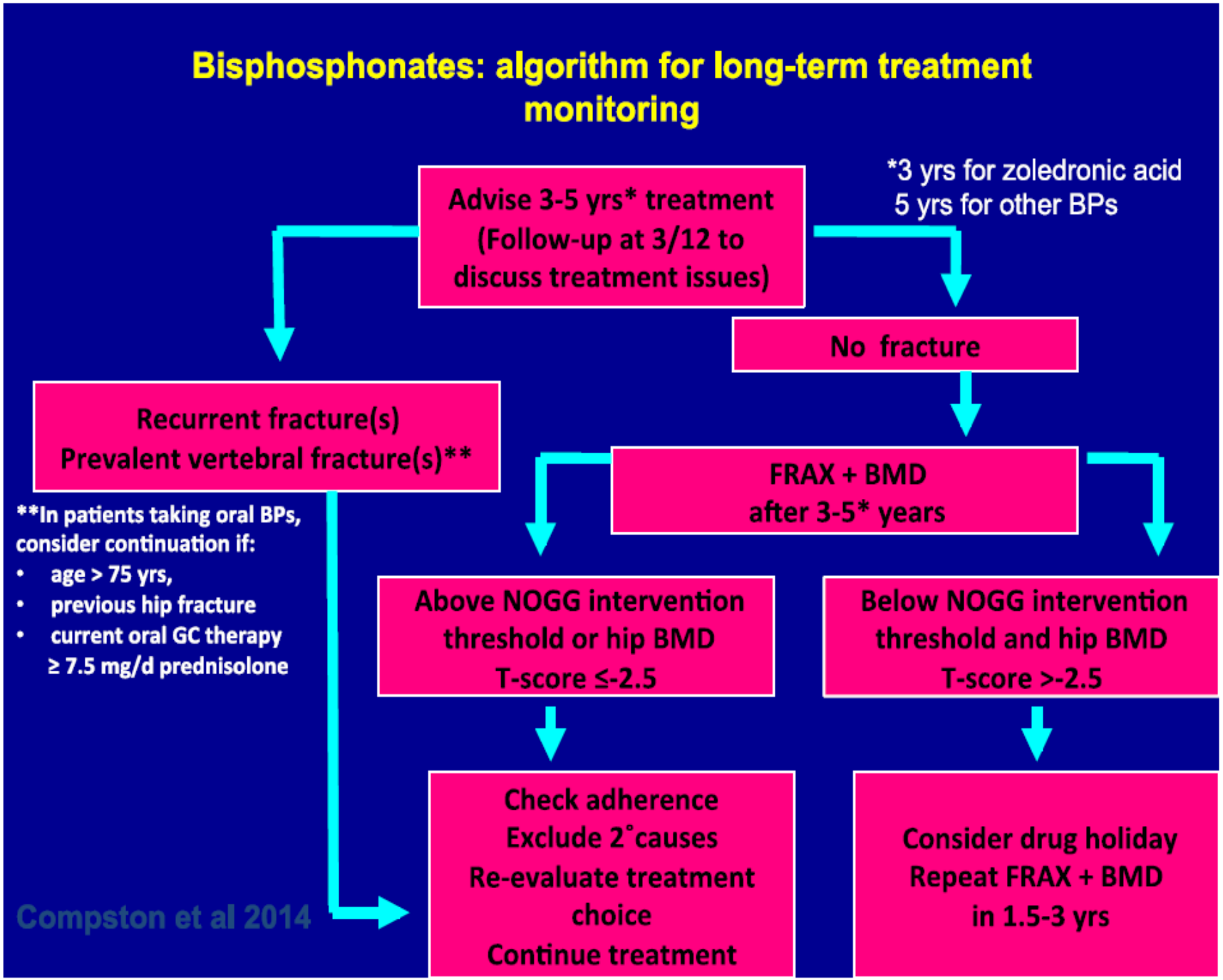
Markery kościotworzenia:

1. Białka macierzy kostnej:
   - osteokalcyna (OC)
   - propeptydy prokolagenu typu I:
     - C-końcowy (PICP)
     - N-końcowy (PINP)
2. Enzymy:
   - fosfataza alkaliczna – izoenzym kostny (bALP)

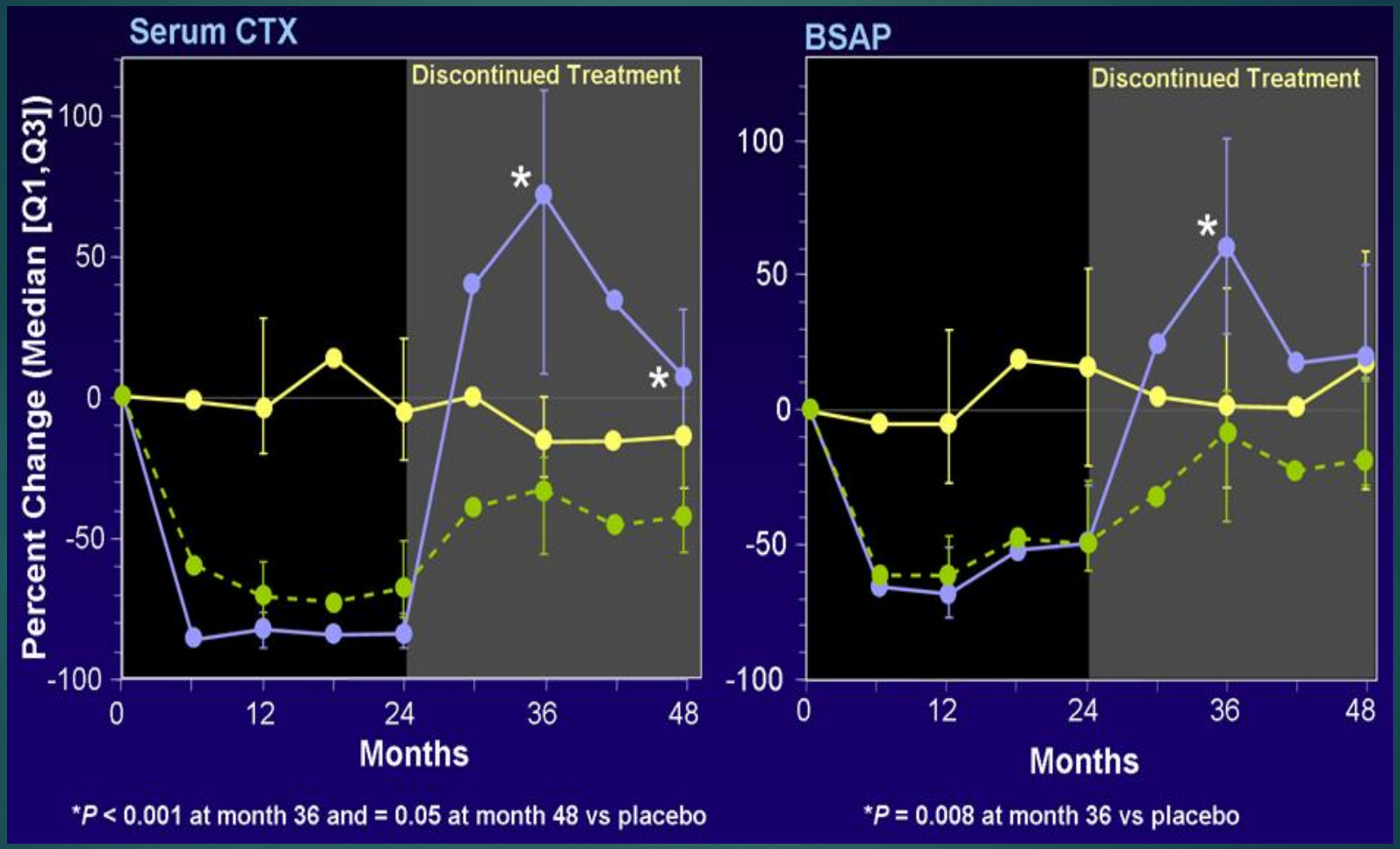
Markery resorpcji kostnej:

1. Produkty degradacji kolagenu typu I:
   - usieciowane telopeptydy:
     - C-końcowe (CTx, ICTP)
     - N-końcowy (NTx)
   - wiązania sieciujące: pirydynolina i deoksypirydynolina (Pyr, DPyr)
   - aminokwasy: hydroksyprolina, galaktozylo-hydroksylizyna (HPro, G
2. Enzymy:
   - winianooporna kwaśna fosfataza – izoenzym 5b (TRAP5b)

Zlecenie oznaczen P1NP, CTX , 25(OH)D metoda automatyczną w 1 próbce surowicy


Bisphosphonates: algorithm for long-term treatment monitoring
Advise 3-5 yrs* treatment (Follow-up at 3/12 to discuss treatment issues)
*3 yrs for zoledronic acid
5 yrs for other BPs
No fracture
Recurrent fracture(s)
Prevalent vertebral fracture(s)**
FRAX + BMD after 3-5* years
**In patients taking oral BPs, consider continuation if:
• age > 75 yrs,
• previous hip fracture
• current oral GC therapy ≥ 7.5 mg/d prednisolone
Above NOGG intervention threshold or hip BMD T-score ≤-2.5
Below NOGG intervention threshold and hip BMD T-score >-2.5
Check adherence
Exclude 2˚causes
Re-evaluate treatment choice
Continue treatment
Consider drug holiday
Repeat FRAX + BMD in 1.5-3 yrs
Compston et al 2014

Efektywność leczenia ALN lub DSB:



FOUNDATION for NIH

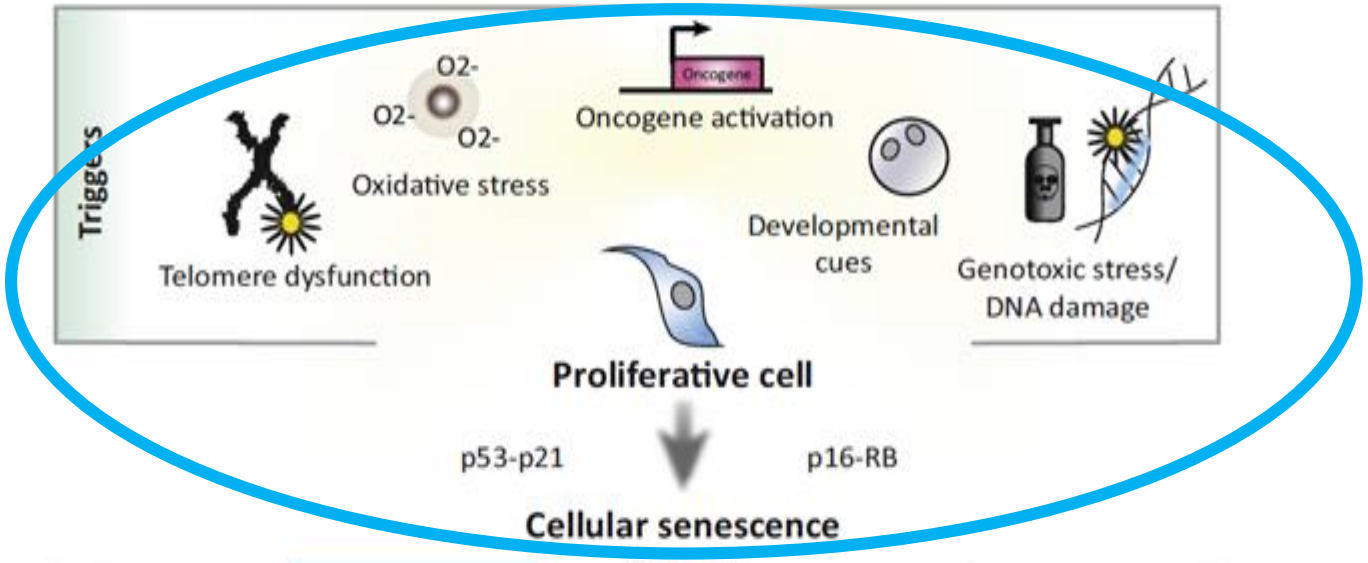
Evaluation and qualification of BTM in the past trials.

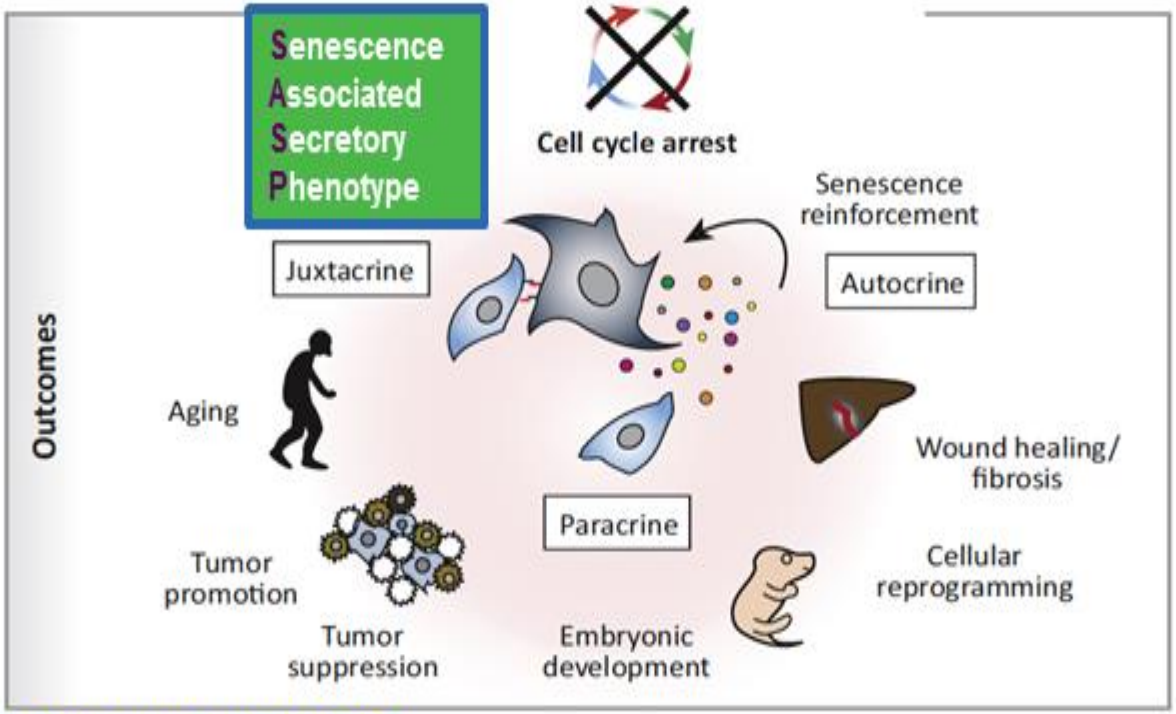
Info released in ASBMR, Denver 2017

PROCESY STARZENIA SIĘ

WIODĄCY "HOT TOPIC" W WYKŁADZIE WPROWADZAJĄCYM R.BARONA,J.CAMPISI WYKŁAD PLENARNY,S.MONOLAGOS WYKŁAD PLENARNY
DONIESIENIA ZJAZDOWE

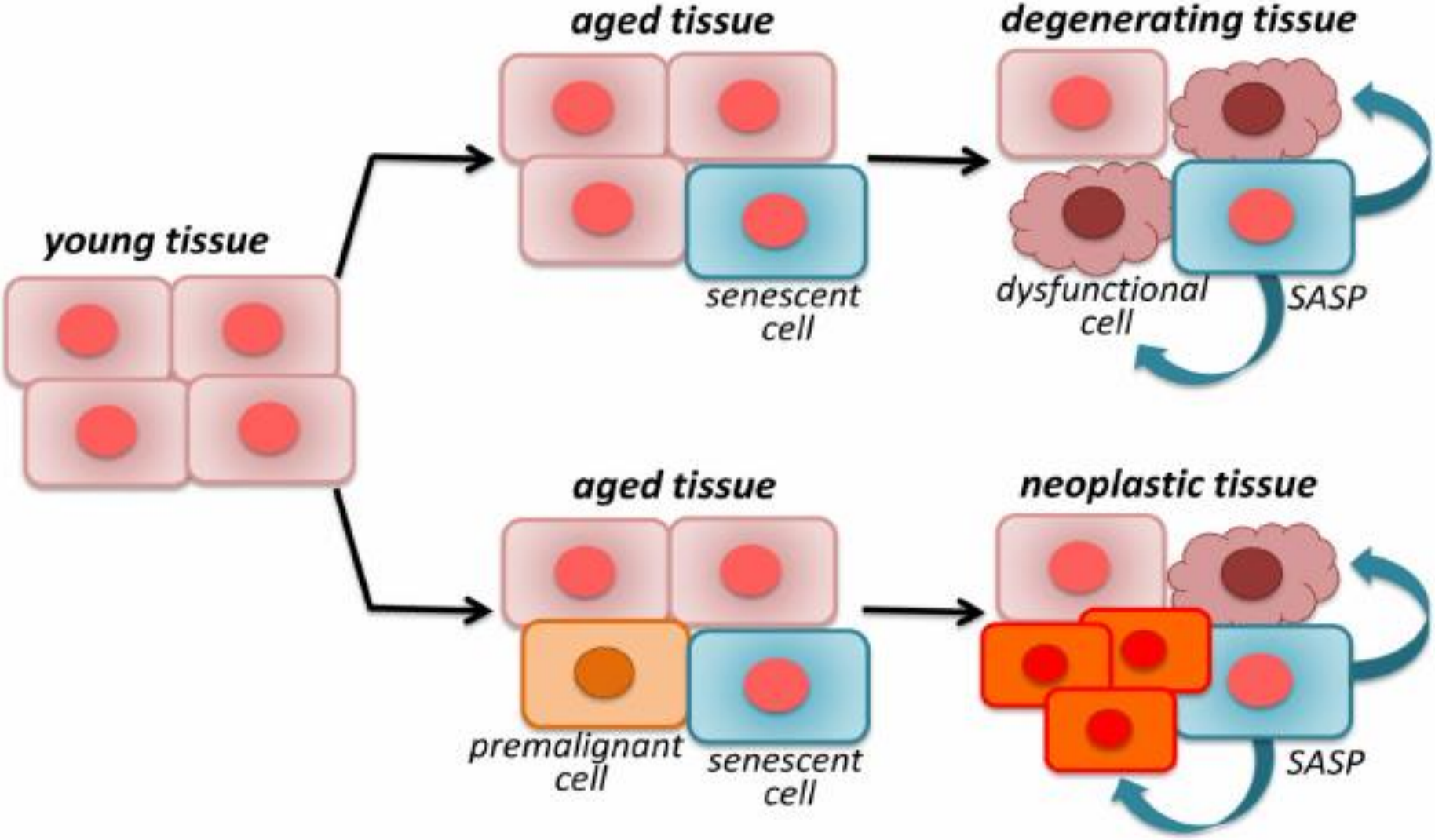
Cellular Senescence



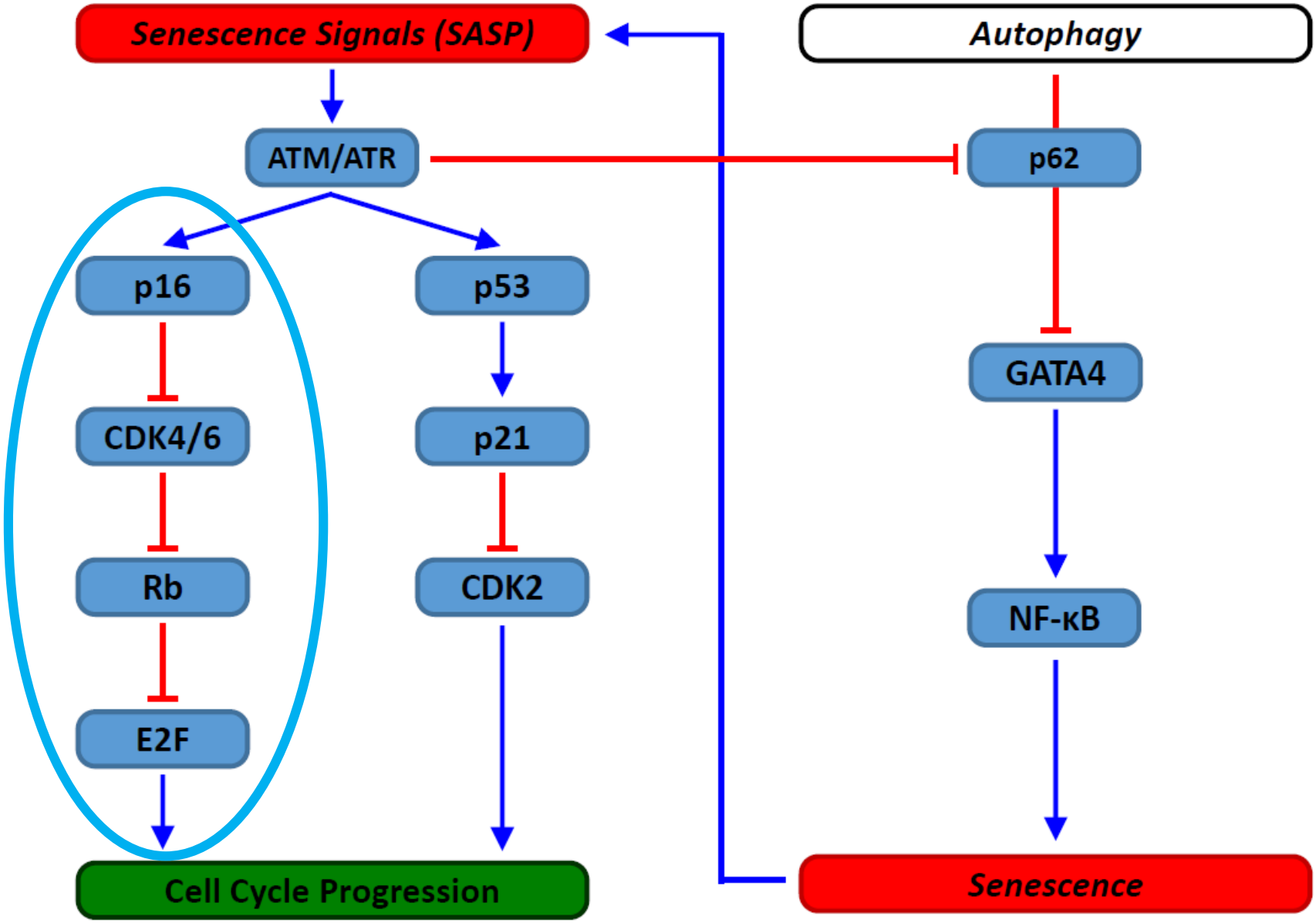


Adapted from Ito et al. *Trends in Cell Biol.* 2017.

PROCESY STARZENIA

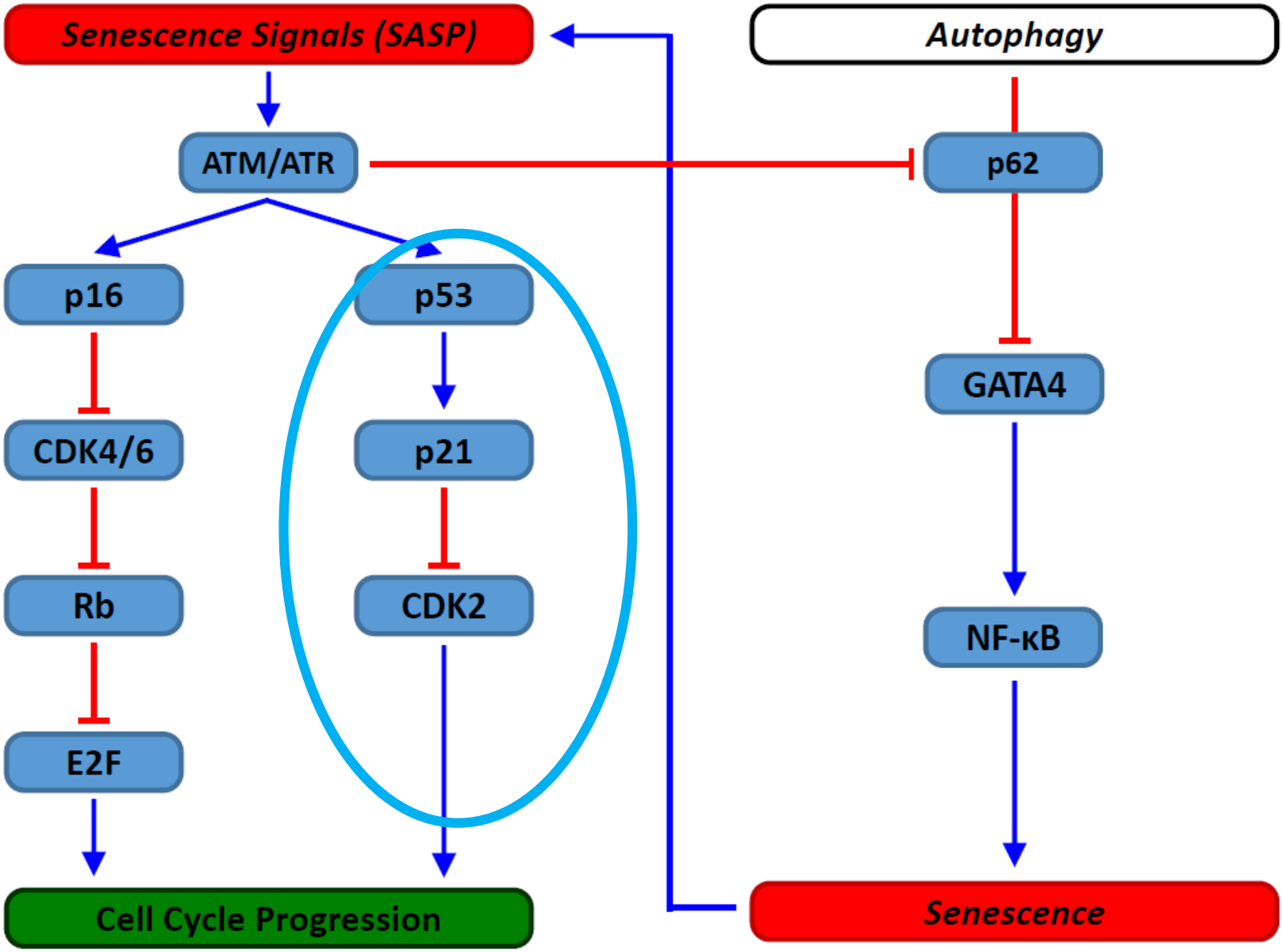


Cellular Senescence Regulatory Pathway

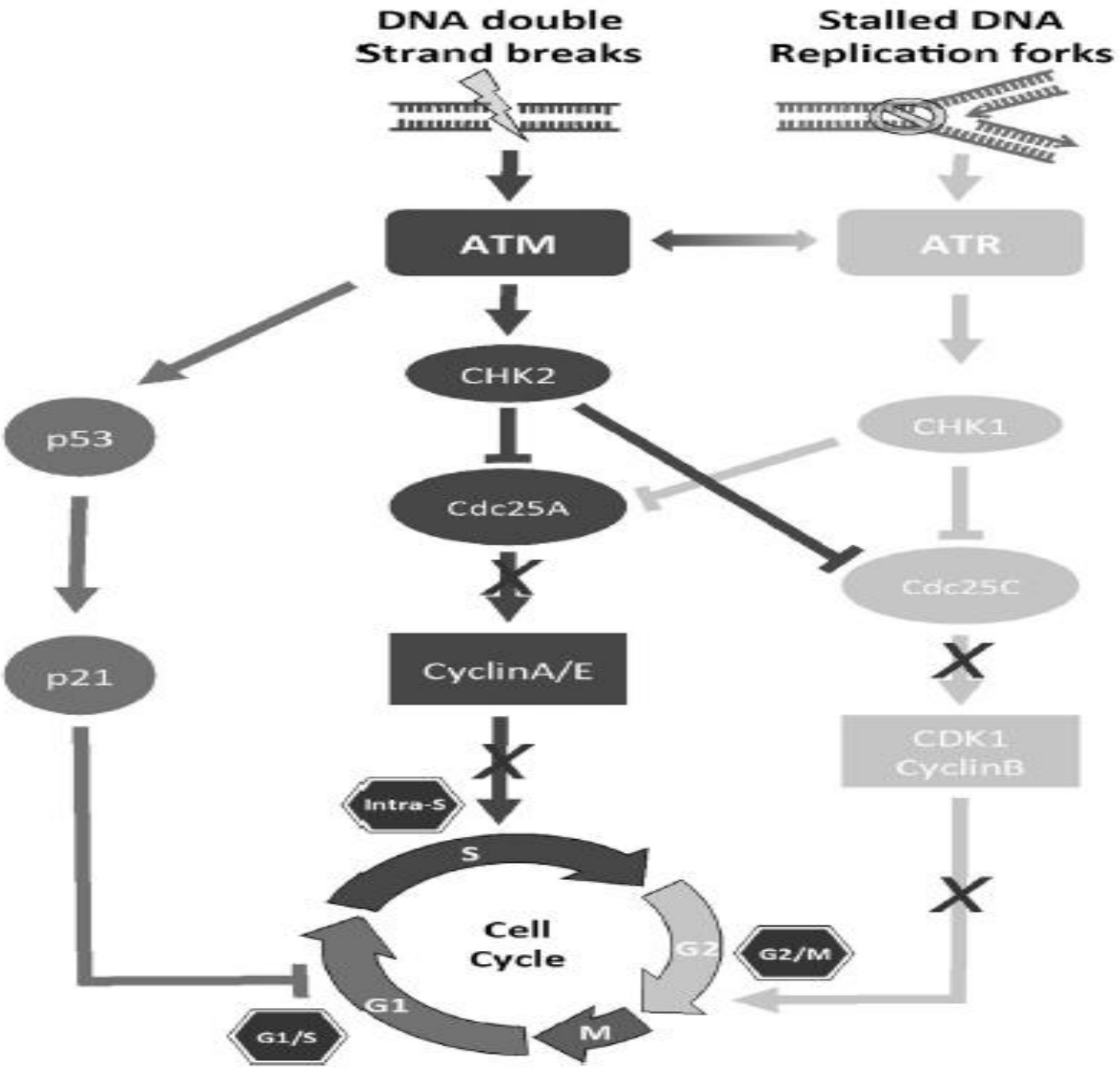


Kang et al. *Science* **2015**, In Press.

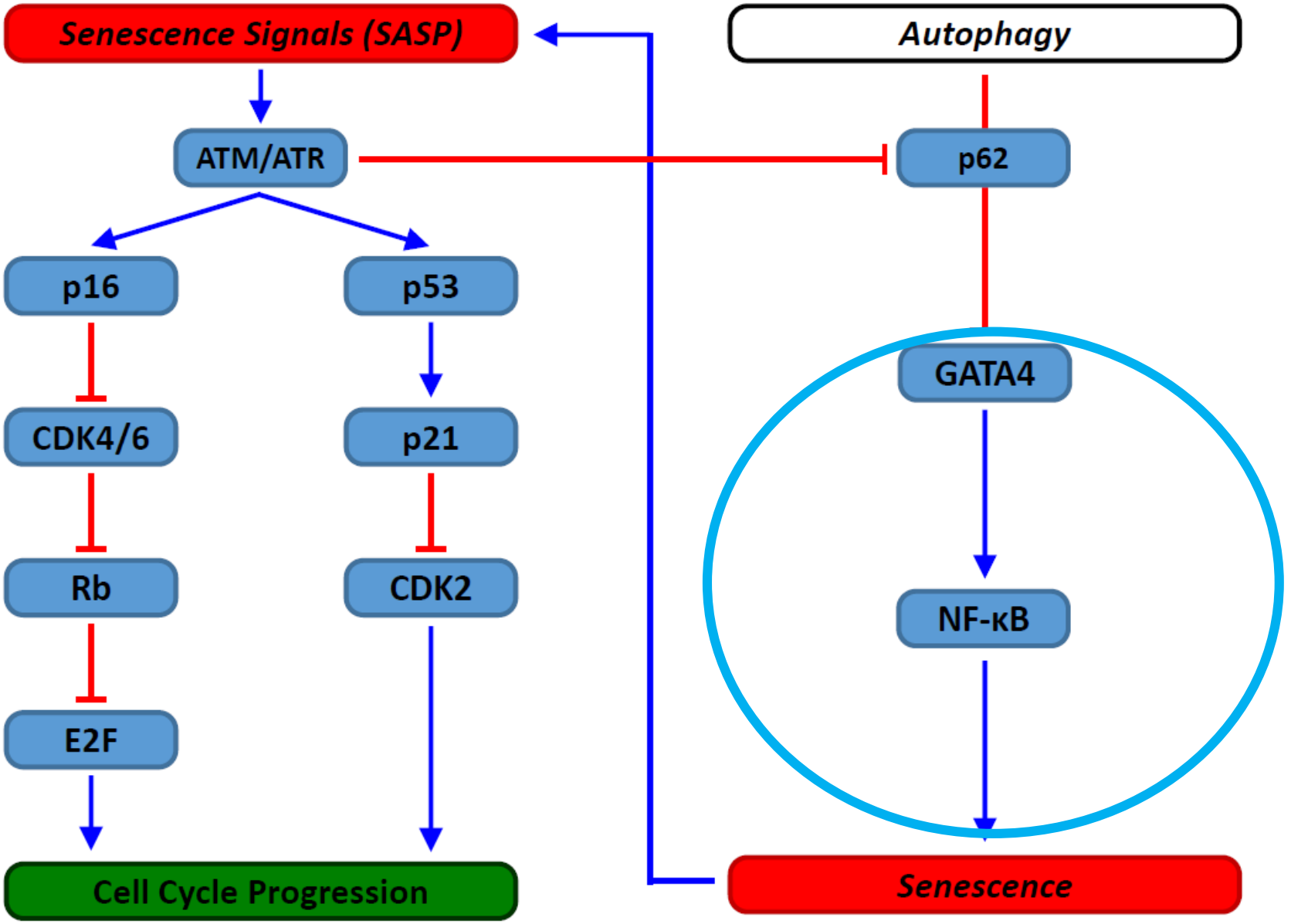
Cellular Senescence Regulatory Pathway



Kang et al. *Science* **2015**, In Press.

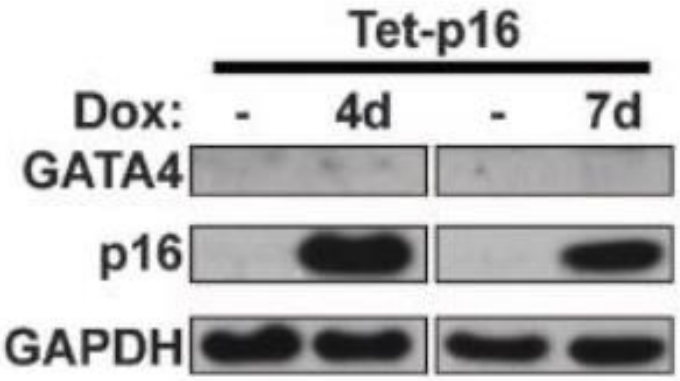

DNA double
Strand breaks
Stalled DNA
Replication forks
ATM
ATR
CHK2
CHK1
p53
Cdc25A
Cdc25C
p21
CyclinA/E
CDK1
CyclinB
Intra-S
S
Cell
Cycle
G2
G2/M
G1
M
G1/S

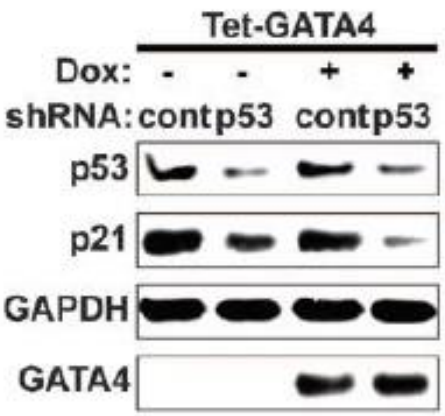
Cellular Senescence Regulatory Pathway

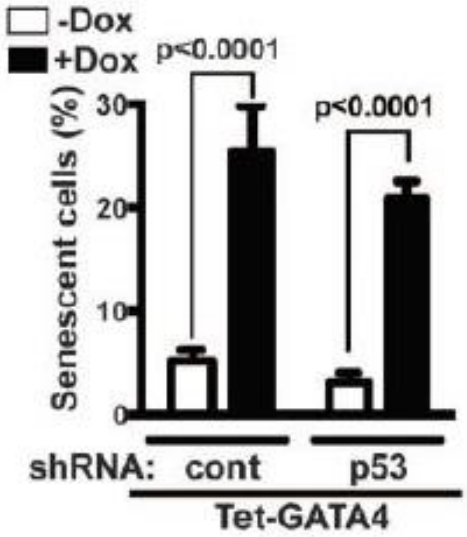


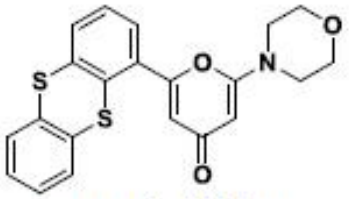
Kang et al. *Science* **2015**, In Press.

GATA4 Regulation Independent of p53, p16

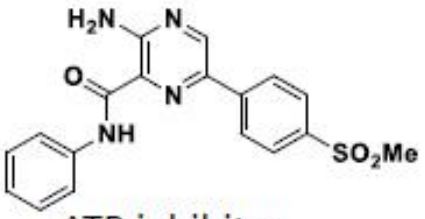




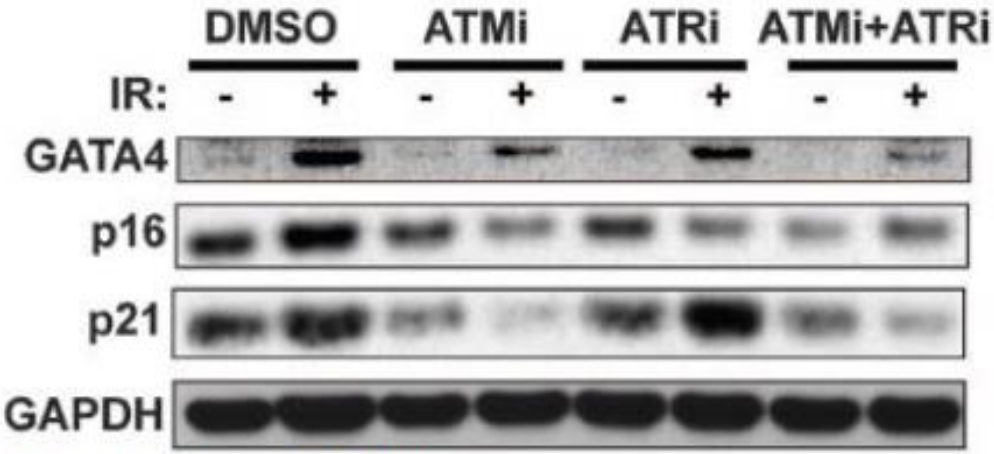




ATM inhibitor



ATR inhibitor



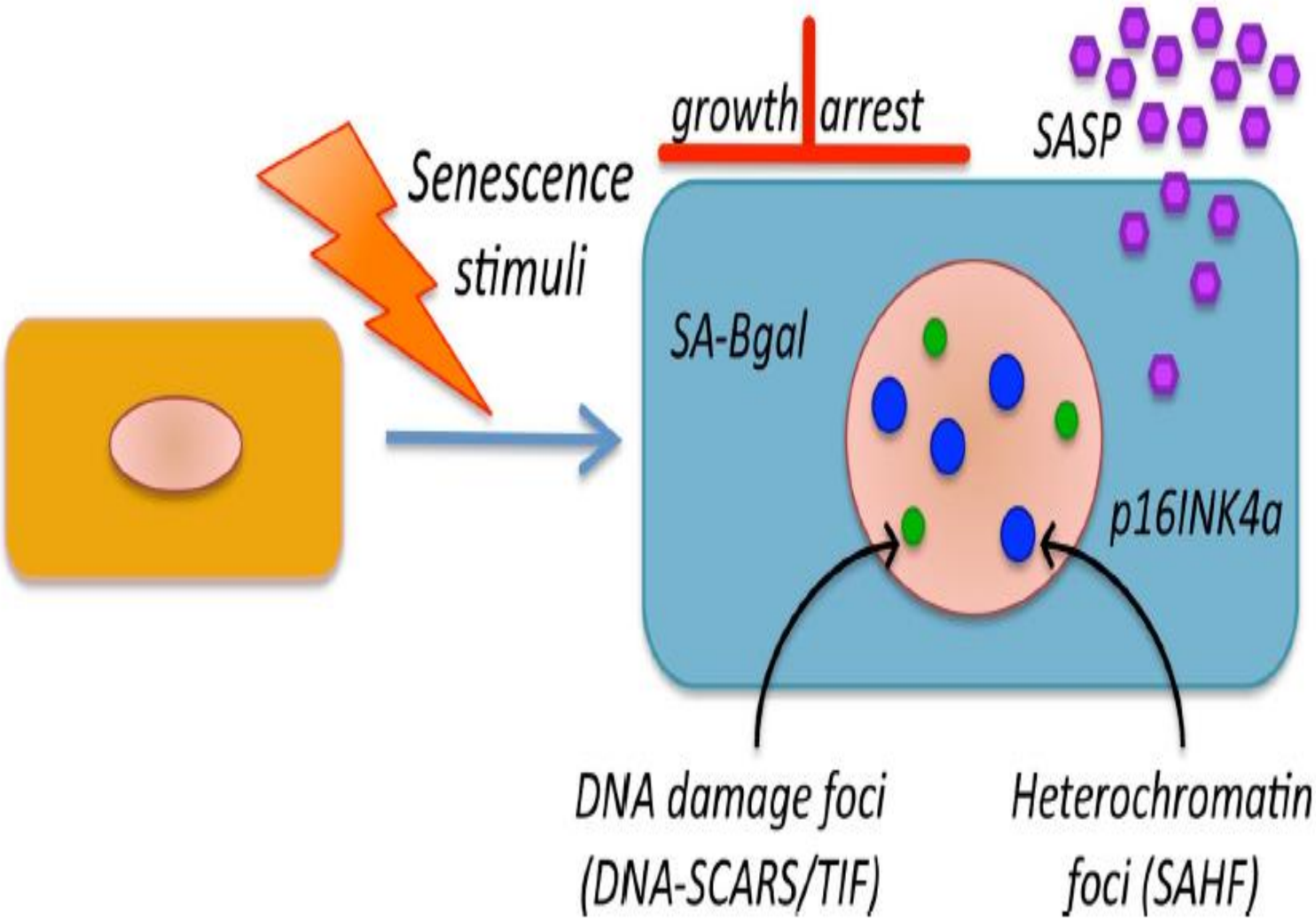
Kang et al. *Science* **2015**, In Press.

1. p16 overexpression in healthy cells did not induce GATA4 expression nor promote senescence.

2. Silencing of p53 or p21 did not significantly decrease GATA4 levels in senescent cells.

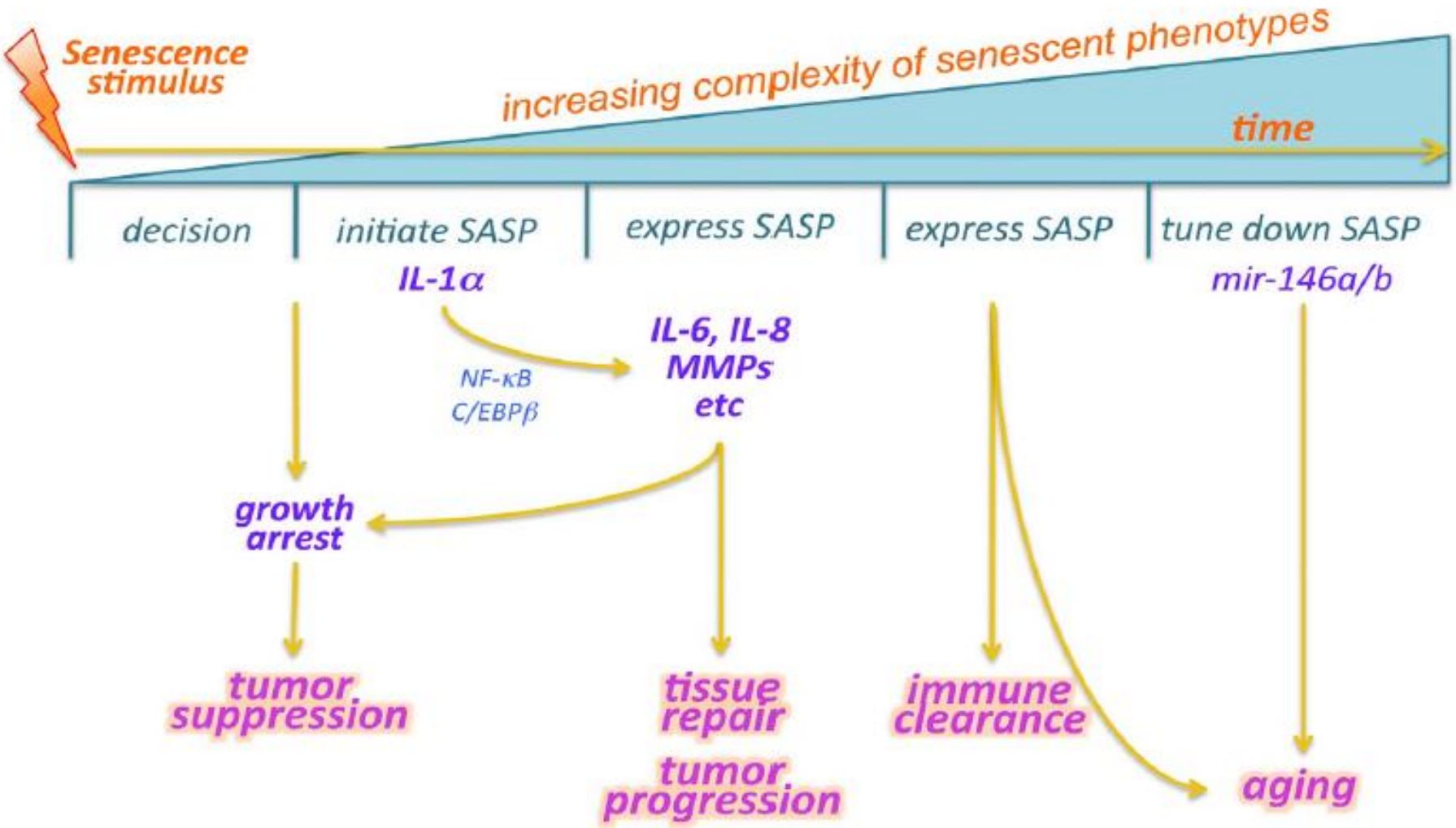
3. Chemical inhibition of ATM and ATR decreased GATA4 levels.

PROCESY STARZENIA
wg.Rodier,Campisi 2011

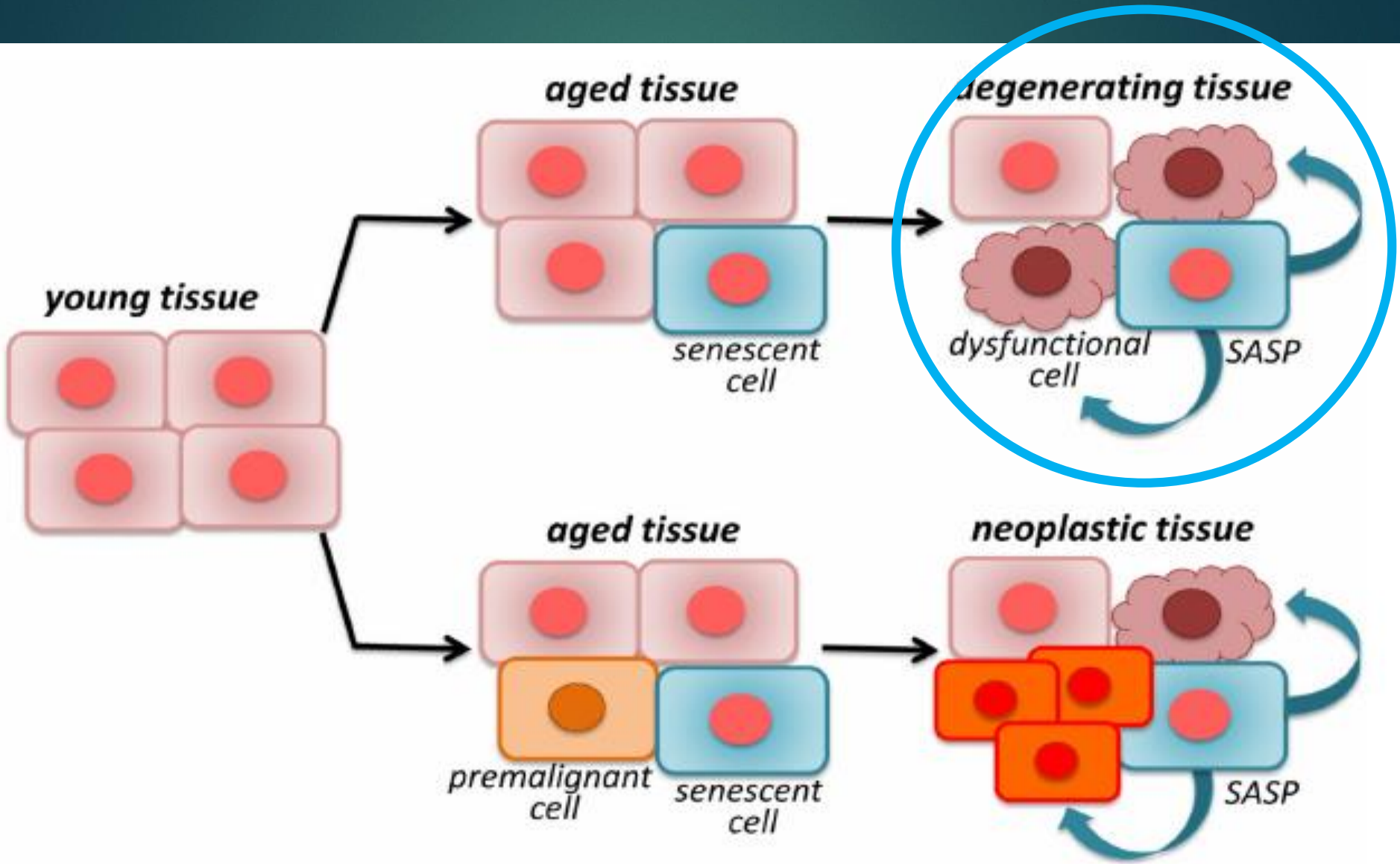


DYNAMIKA PROCESÓW STARZENIA

wg Campisi et al. 2017



PROCESY STARZENIA



UDOKUMENTOWANY UDZIAL "SENESCENCE CELLS" W PATOLOGIACH OGOLNOUSTROJOWYCH wg.J.Campisi 2017

1. Miazdzyca
2. Schorzenia ukladu krążenia
3. Przerzuty nowotworowe
4. Chemioterapia
5. Kardiotoksyczność
6. Osteoartroza
7. Osteoporoza
8. Regeneracja komórek
9. Gojenie ran

ASBMR 2017 Annual Meeting
September 8–11, 2017
Colorado Convention Center
Denver, Colorado, USA
asbmr2017.org

[1042] Causal Role of Senescent Cells in Mediating Age-Related Bone Loss

Joshua Farr, Mayo Clinic,
September 9, 09:45 AM - 10:00 AM
Mile High Ballroom/Colorado Convention Center
Session:Plenary Orals: Translational Plenary 1

1042: Causal Role of Senescent Cells in Mediating Age-Related Bone Loss

ASBMR 2017 Annual Meeting
#ASBMR2017

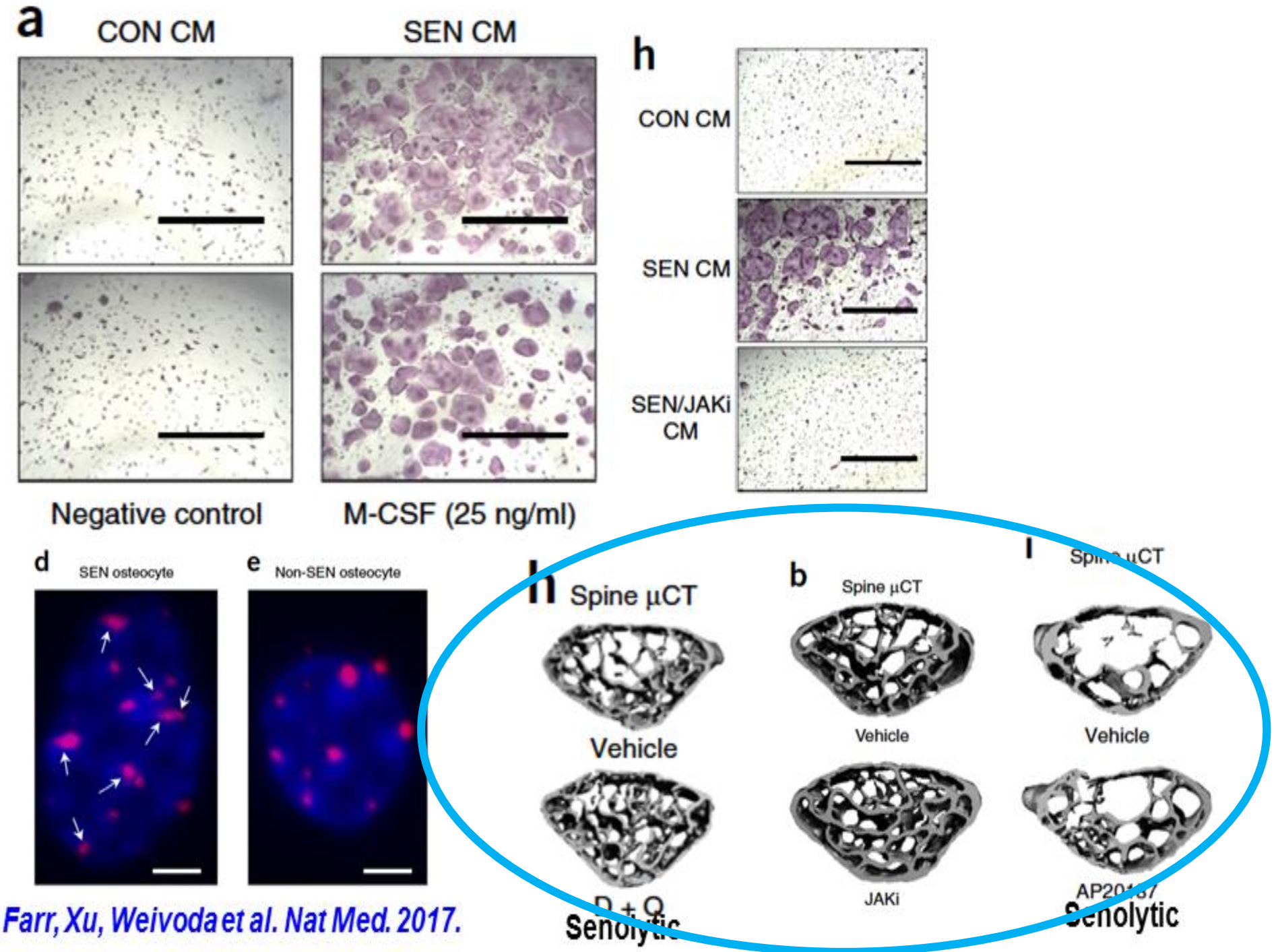
Authors: Joshua Farr, James Kirkland, Sundeep Khosla; Mayo Clinic

Most Outstanding Translational Abstract

Accumulation of DNA damage and stressors cause induces **cell senescence**, with increased cell cycle inhibitor, p16Ink4a and **production of SASP**, with deleterious paracrine and systemic effects.

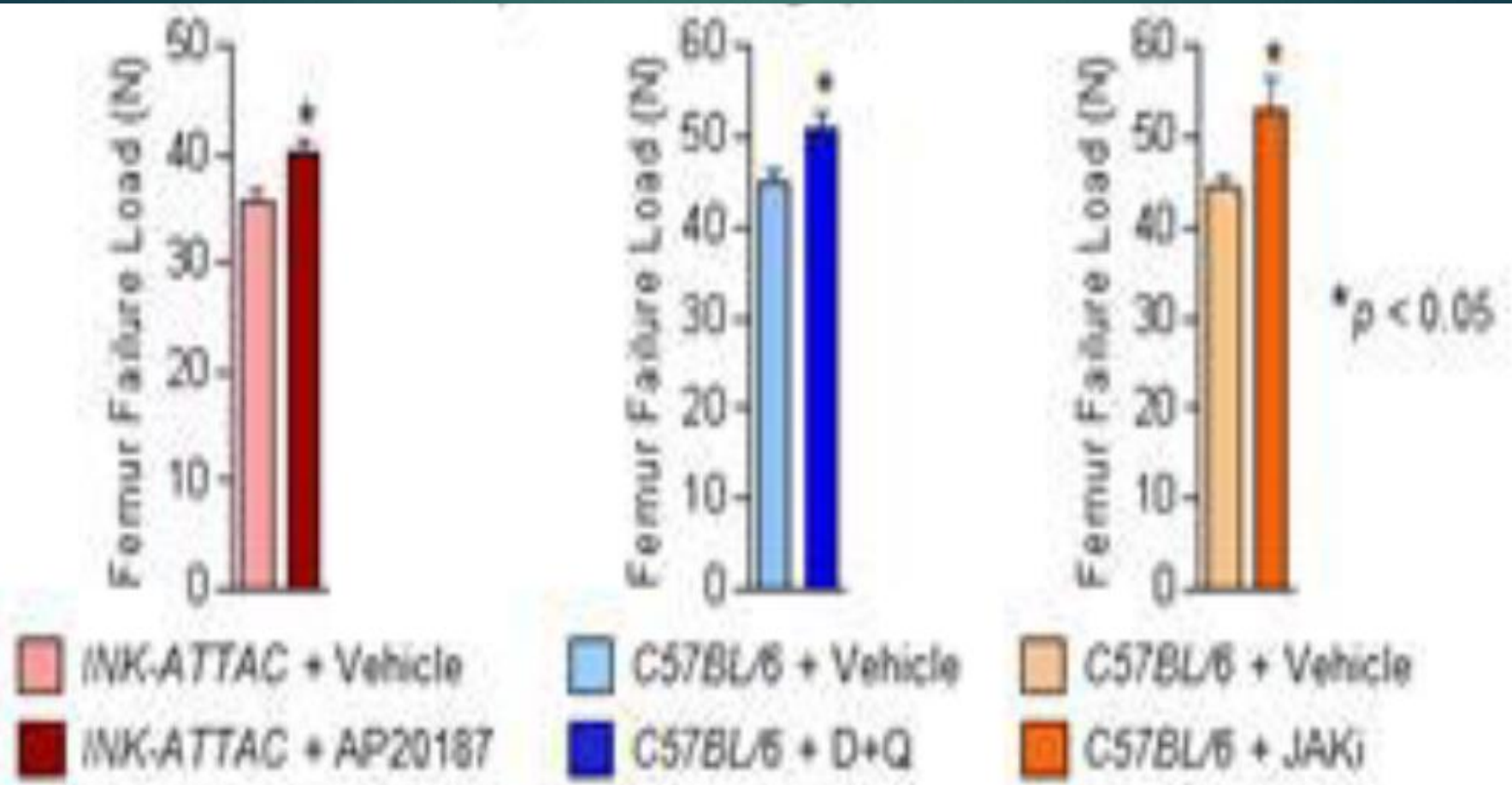
Question: **What is the role of senescent cells in age-related bone loss?**

- 3 strategies: 1) **reducing senescent cell number** in mice using the inducible INK-ATTAC "suicide" transgene 2) **clearing senescent cells by "senolytic" compounds**; or 3) **inhibiting SASP** production with a **JAK inhibitor** (JAKi).
- In old (20-22 month) mice with bone loss, **2-4 month treatment with each of these interventions improved bone mass and strength by suppressing bone resorption** with either **maintaining (trabecular bone) or increasing (cortical bone) bone formation**.
- **In vitro, senescent cell CM impaired OB mineralization and enhanced OC progenitor survival**, leading to **increased OCgenesis, abrogated by pre-treatment with JAKi**.
- Specificity to aging was shown by **absence of skeletal effects in young (7-12 month-old) mice**.



Farr, Xu, Weivoda et al. Nat Med. 2017.

Micro-finite element analysis (μFEA)-derived failure load (*i.e.*, bone strength)



ASBMR 2017 Annual Meeting

September 8–11, 2017
Colorado Convention Center
Denver, Colorado, USA
asbmr2017.org

[1027] The Senolytic ABT263 Eliminates Senescent Osteoprogenitors in Old Mice

Ha-Neui Kim, University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System,

September 8, 02:15 PM - 02:30 PM
Four Seasons Ballroom II-III/Colorado Convention Center
Session:Concurrent Orals: Osteoporosis Pathophysiology

ASBMR 2017 Annual Meeting
#ASBMR2017

 # 1027:The Senolytic ABT263 Eliminates Senescent Osteoprogenitors in Old Mice

Authors: Ha-Neui Kim; Maria Almeida; University of Arkansas;

Conclusion: **GATA4 in osteoprogenitors of old mice contributes to cell senescence and expression of the SASP. Removal of senescent cells with senolytic agents decreased RANKL and improved OBgenesis, possibly representing a novel therapeutic approach to osteoporosis.**
Kim et al. Aging Cell, 2017

Conclusion: **Senescent cells play a causal role in bone loss with aging**. Eliminating senescent cells and/or inhibiting SASP also improves CV function, insulin sensitivity, and reduces frailty. Thus, this approach reveals a **novel treatment strategy for osteoporosis and simultaneously treat multiple age-related co-morbidities**.

Farr, Xu, Weivoda et al. Nat Med, 2017

Suppression of Autophagy in Osteocytes Mimics Skeletal Aging*[S]

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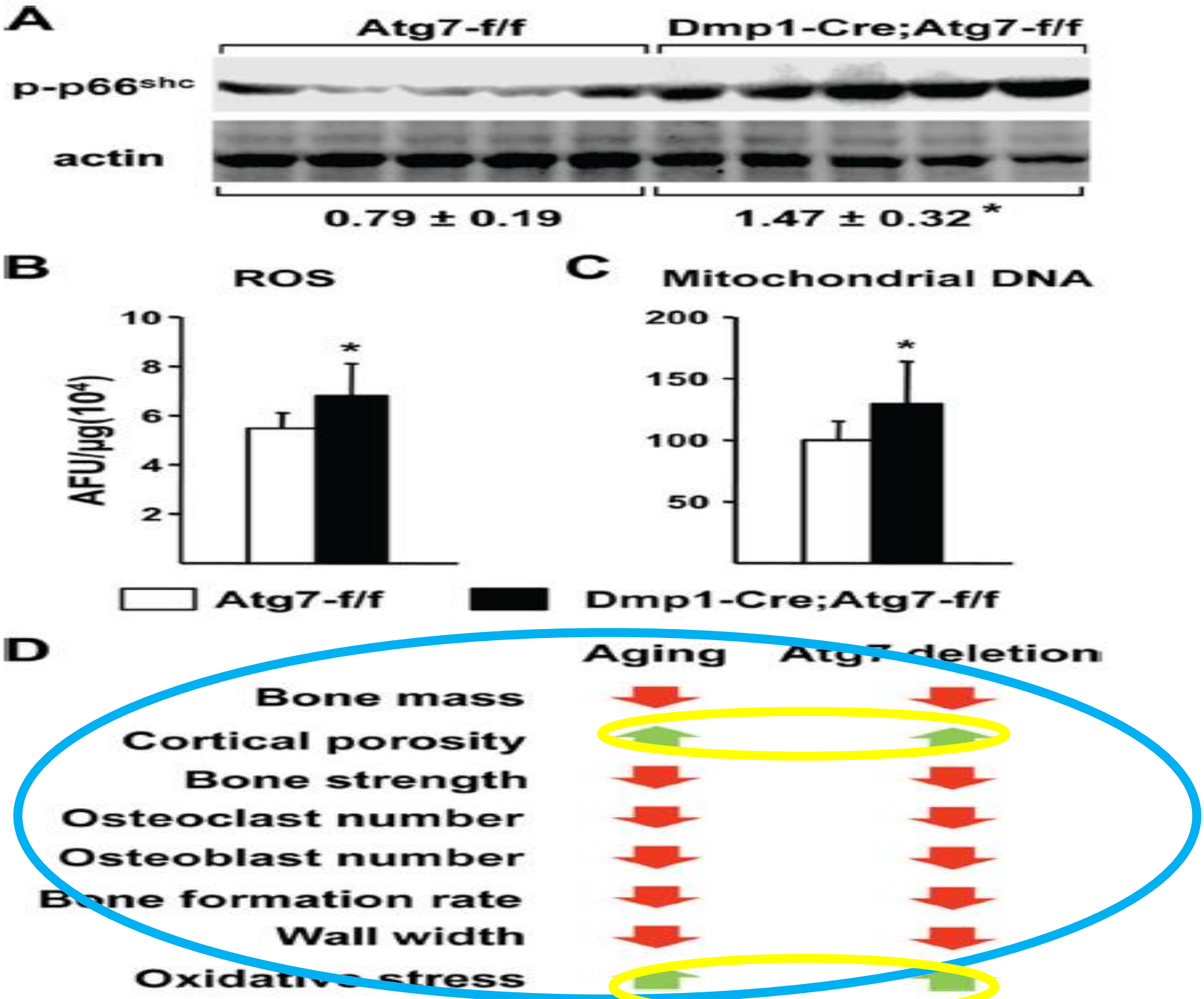
Background: The role of autophagy in osteocytes is unclear.

Results: Suppression of autophagy in osteocytes caused decreases in bone mass and bone remodeling similar to those caused by aging.

Conclusion: Autophagy in osteocytes maintains the rate of remodeling and bone mass.

Significance: A decline in autophagy in osteocytes may contribute to skeletal aging.

Osteocyte Autophagy Maintains Bone Mass



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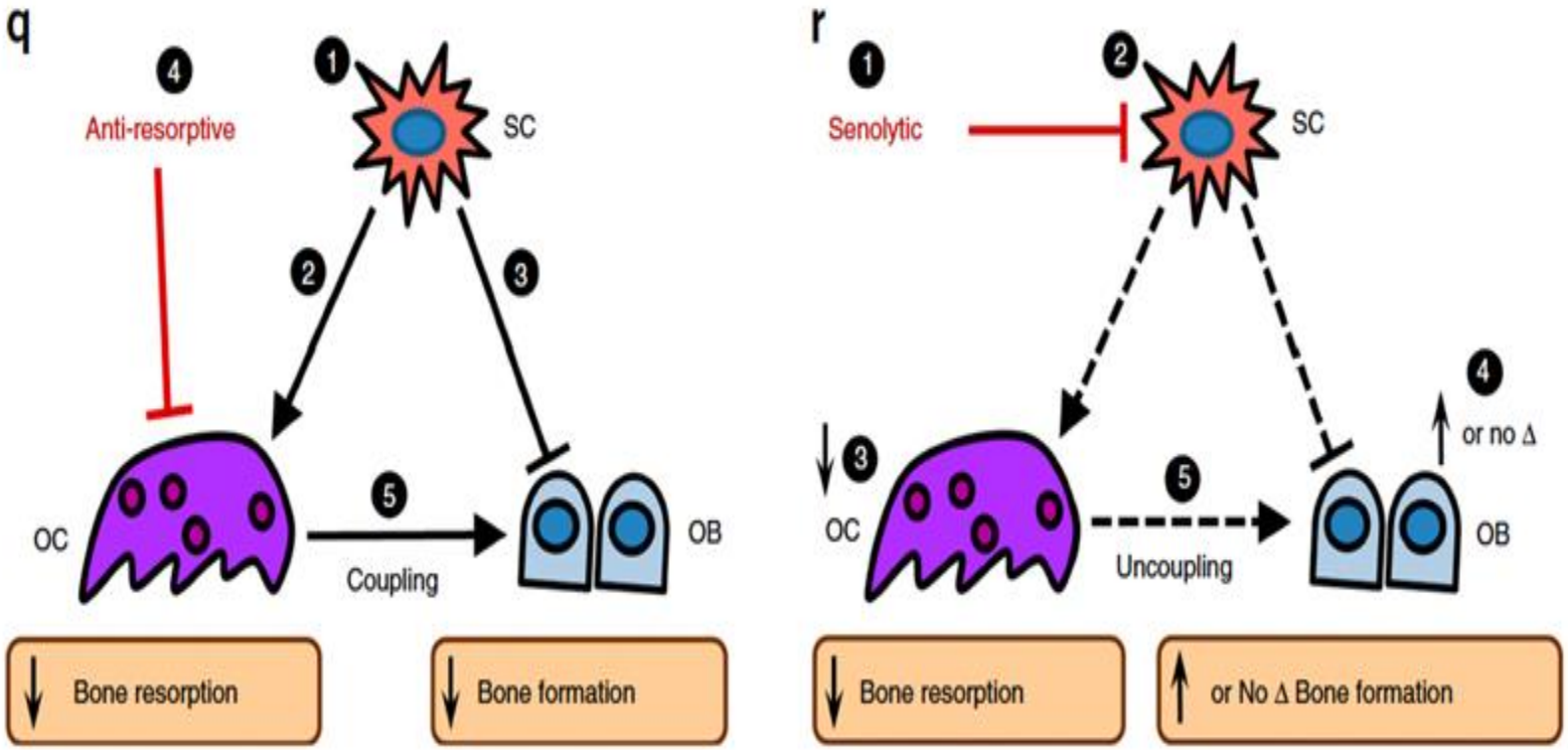
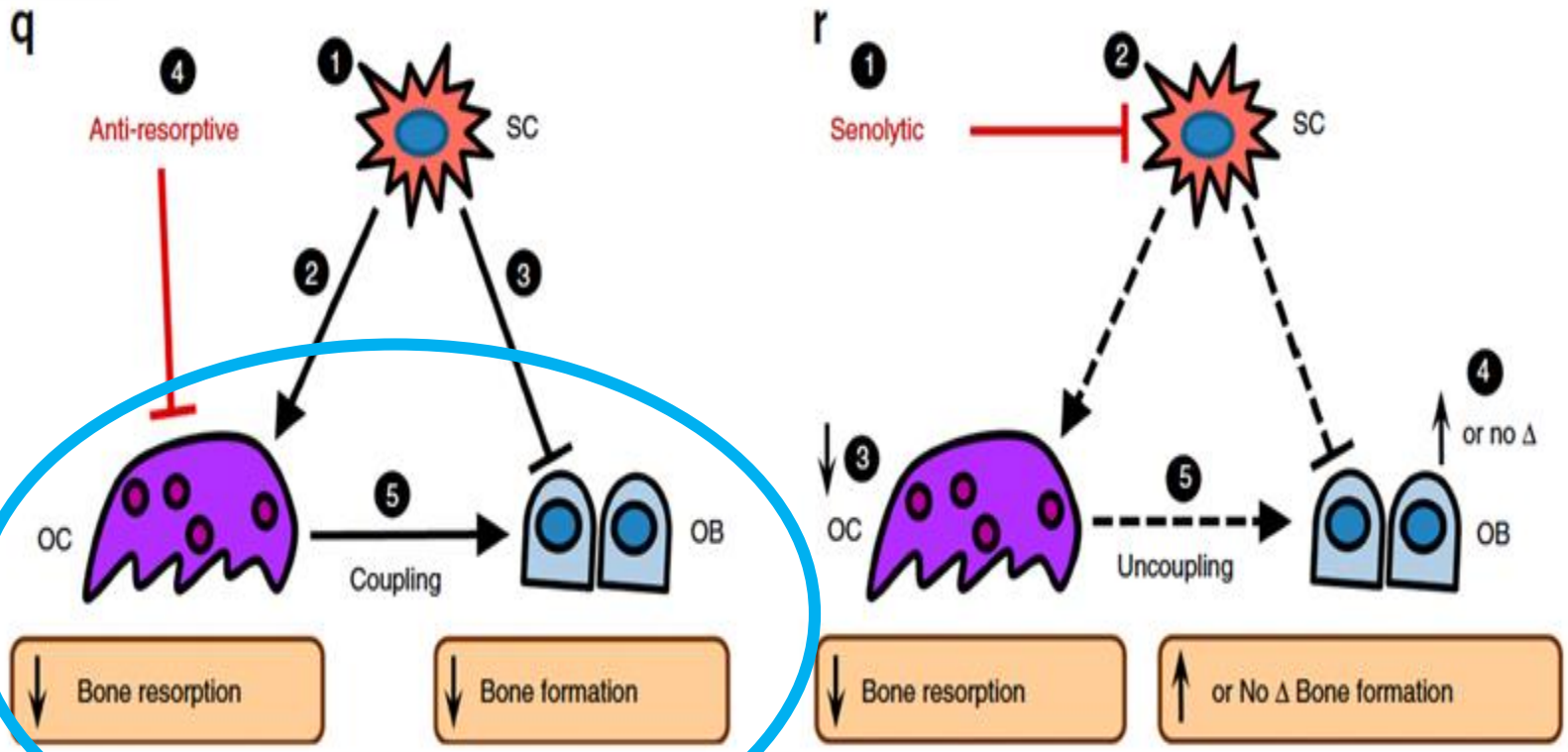


Conclusion: **Senescent cells play a causal role in bone loss with aging**. Eliminating senescent cells and/or inhibiting SASP also improves CV function, insulin sensitivity, and reduces frailty. Thus, this approach reveals a **novel treatment strategy for osteoporosis and simultaneously treat multiple age-related co-morbidities**.

Farr, Xu, Weivoda et al. Nat Med, 2017



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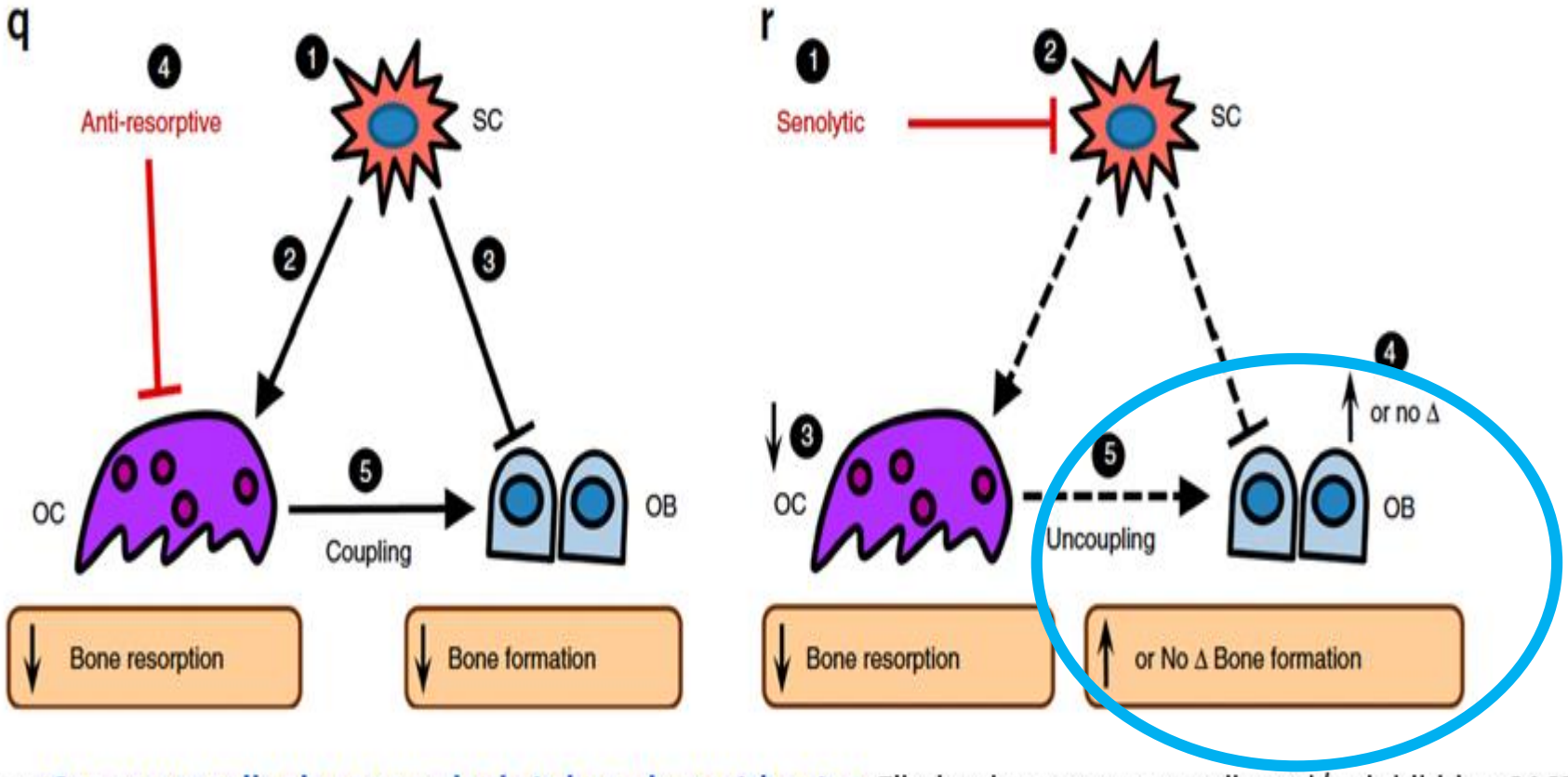

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1.STARZENIE SIĘ TKANKI KOSTNEJ STANOWI ZASADNICZĄ PRZYCZYNĘ NARASTAJĄCYCH ZMIAN DEGENERCYJNYCH AŻ DO WYSTĄPIENIA ZŁAMAŃ

2.PROCESY STARZENIOWE UJAWNIAJĄ SIĘ JAKO WIELORAKIE WEWNĘTRZNE I ZEWNĘTRZNE DYSFUNKCJE TKANKI KOSTNEJ

3.STARZENIE SIĘ KOŚCI PRZEBIEGA NIEZALEŻNE OD NIEDOBORU ESTROGENOW

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