Evidence For and Against Effectiveness of Low Intensity Pulsed Ultrasound for Bone Fracture Healing

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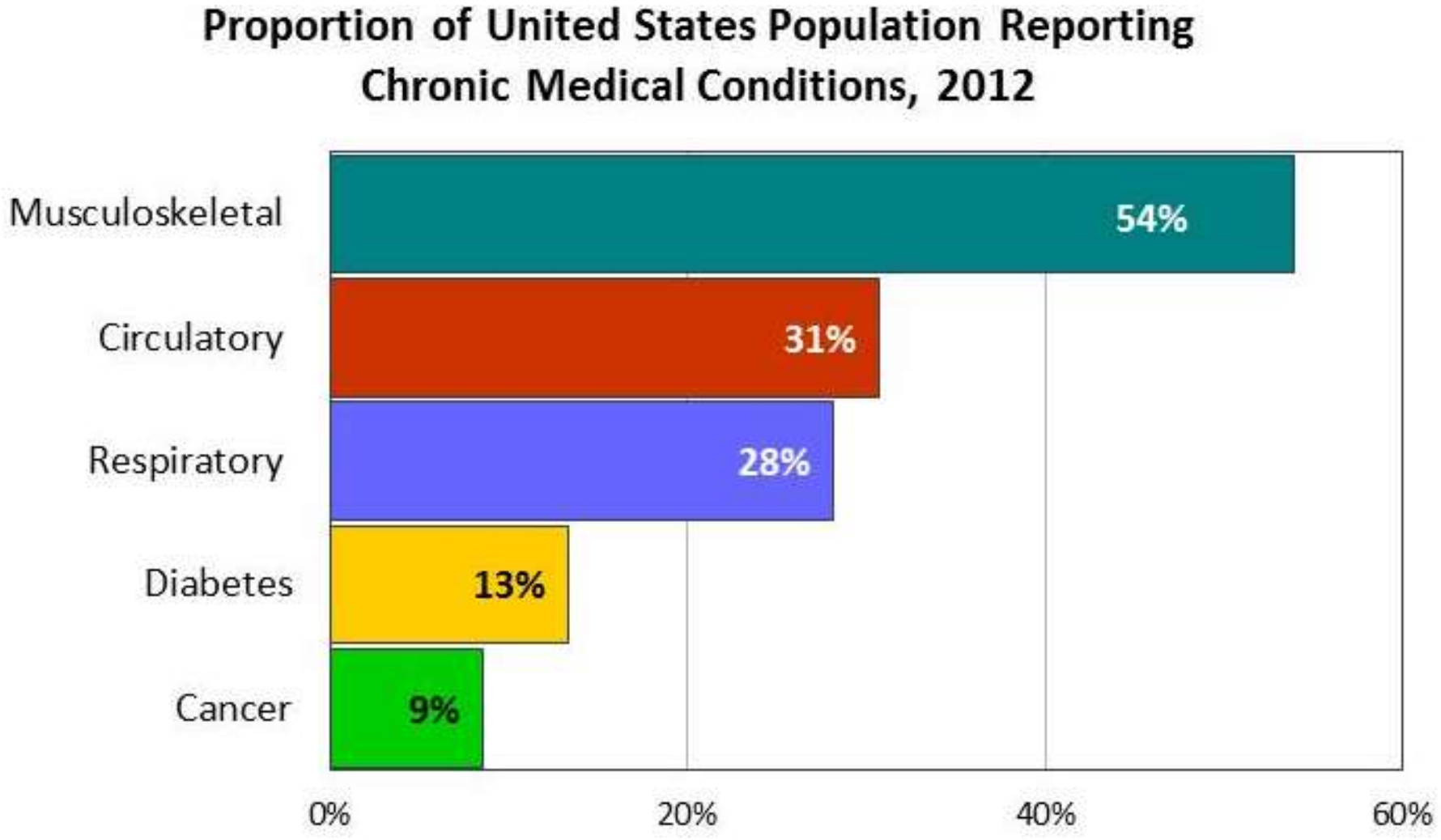
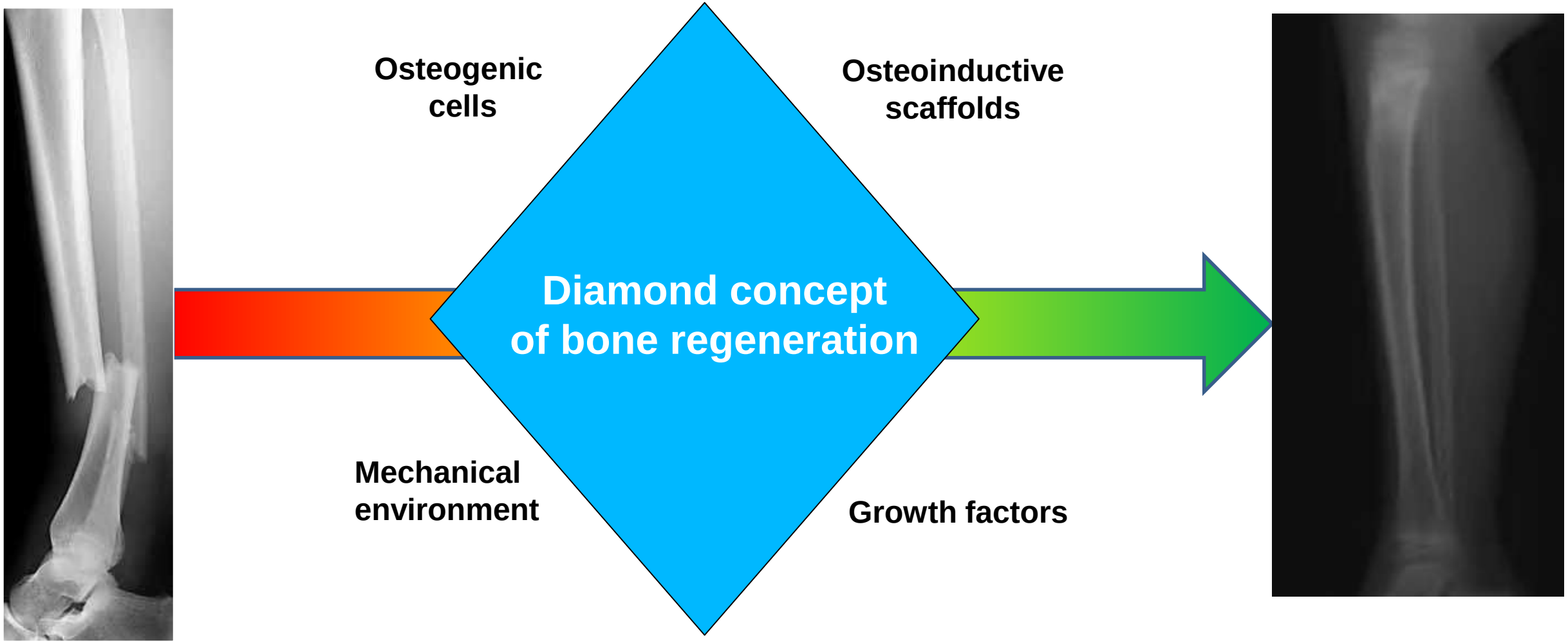
Relevance of musculoskeletal disorders



Source: National Center for Health Statistics, National Health Interview Survey, 2012

Bone Regeneration

- Bone has the unique capacity of **scarless regeneration** & **recovery to full functionality**

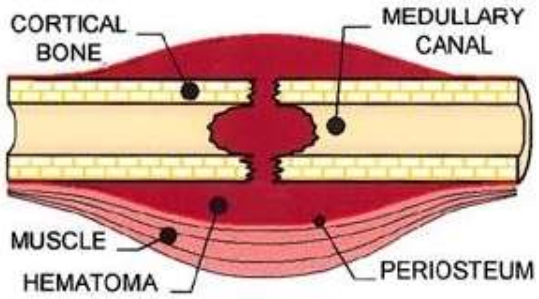


Reproduced from Giannoudis *et al.*, 2007

Phases of Fracture Healing

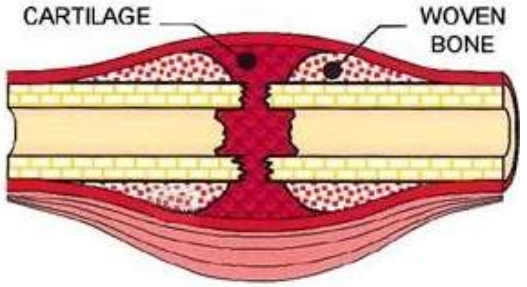
I. **Haematoma** formation, inflammation,

→ recruitment of **osteogenic precursor cells**



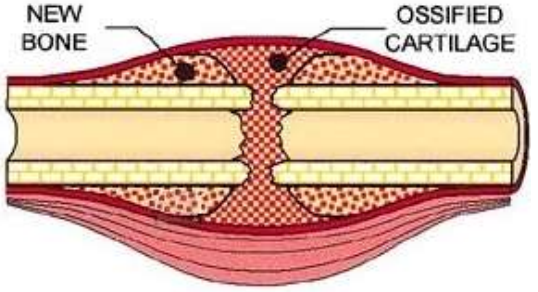
II. **Angiogenesis**, cell proliferation osteogenic differentiation

→ **Intramembranous ossification**



III. Chondrogenesis, maturation of osteoblasts

→ **Endochondral ossification**



IV. Cell maturation

→ **Remodeling**

Bone fracture treatment complications

Tibia shaft fracture

Malunion

Delayed/ nonunions

Infections

Large defects

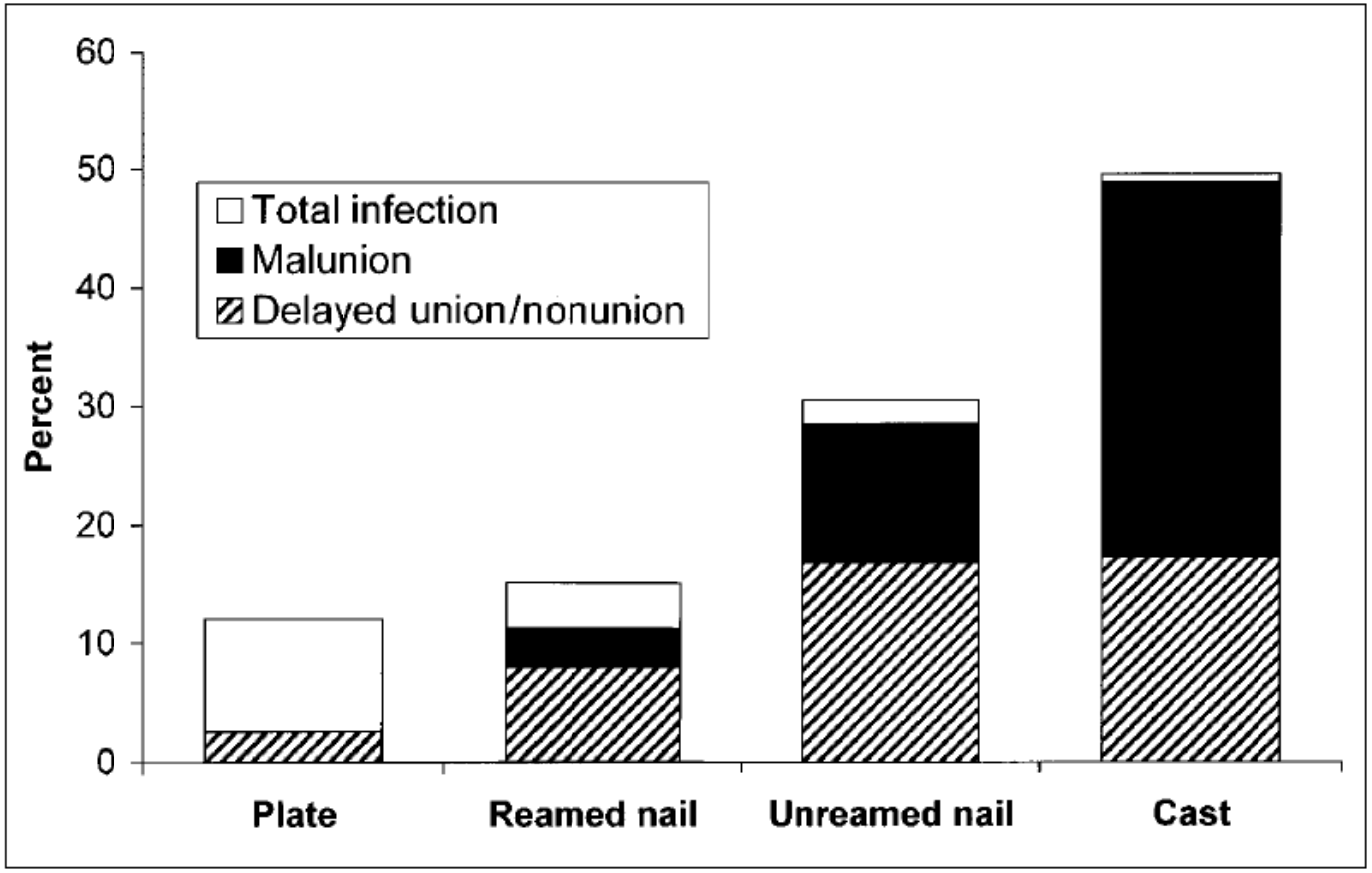


FIG. 5. Combined complications of delayed union, nonunion, malunion and total infection for each treatment method.

Coles & Gross JCC, 2000

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Low Intensity Pulsed Ultrasound

- is an **add-on treatment** and portable **device**

- is used to **promote bone healing** by stimulating bone growth (osteogenesis)

- **applications**
  - operatively or non-operatively managed fractures
  - osteotomies (cutting of a bone)
  - Delayed unions and nonunions

- **costs**
  - $1500 to 7000 USD (purchase)
  - some devices can be re-used
  - Health insurance may or may not cover the cost of the device

Exogen's Sonic Accelerated Fracture Healing System (SAFHS) (Exogen, Inc, Piscataway, NJ)

1994 FDA premarket approval
- *fresh, closed, posteriorly displaced distal radius fractures*
- *fresh, closed or grade I open tibial diaphyseal fractures*

2000
- *established nonunions, excluding skull and vertebra*

Low Intensity Pulsed Ultrasound - Definition

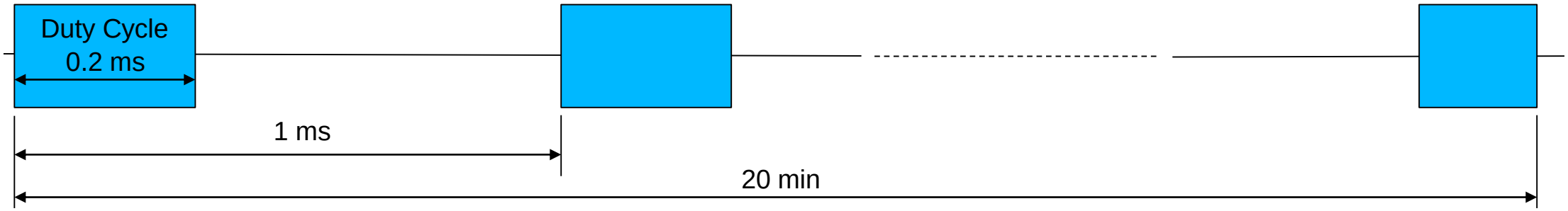
- **Ultrasound** waves with frequencies above the audible range are used

$$100\ \text{kHz} \leq \mathbf{f} \leq 10\ \text{MHz}$$

- **Low Intensity** level (spatially and temporally averaged) between those used for diagnostic and therapeutic ultrasound applications,

$$5\text{mW/cm}^2 \leq \mathbf{I_{sata}} \leq 100\ \text{mW/cm}^2$$

- **Pulsed** bursts of acoustic waves are applied at a Pulse Repetition Frequency (PRF) and Duty Cyle (DC) for a specific time



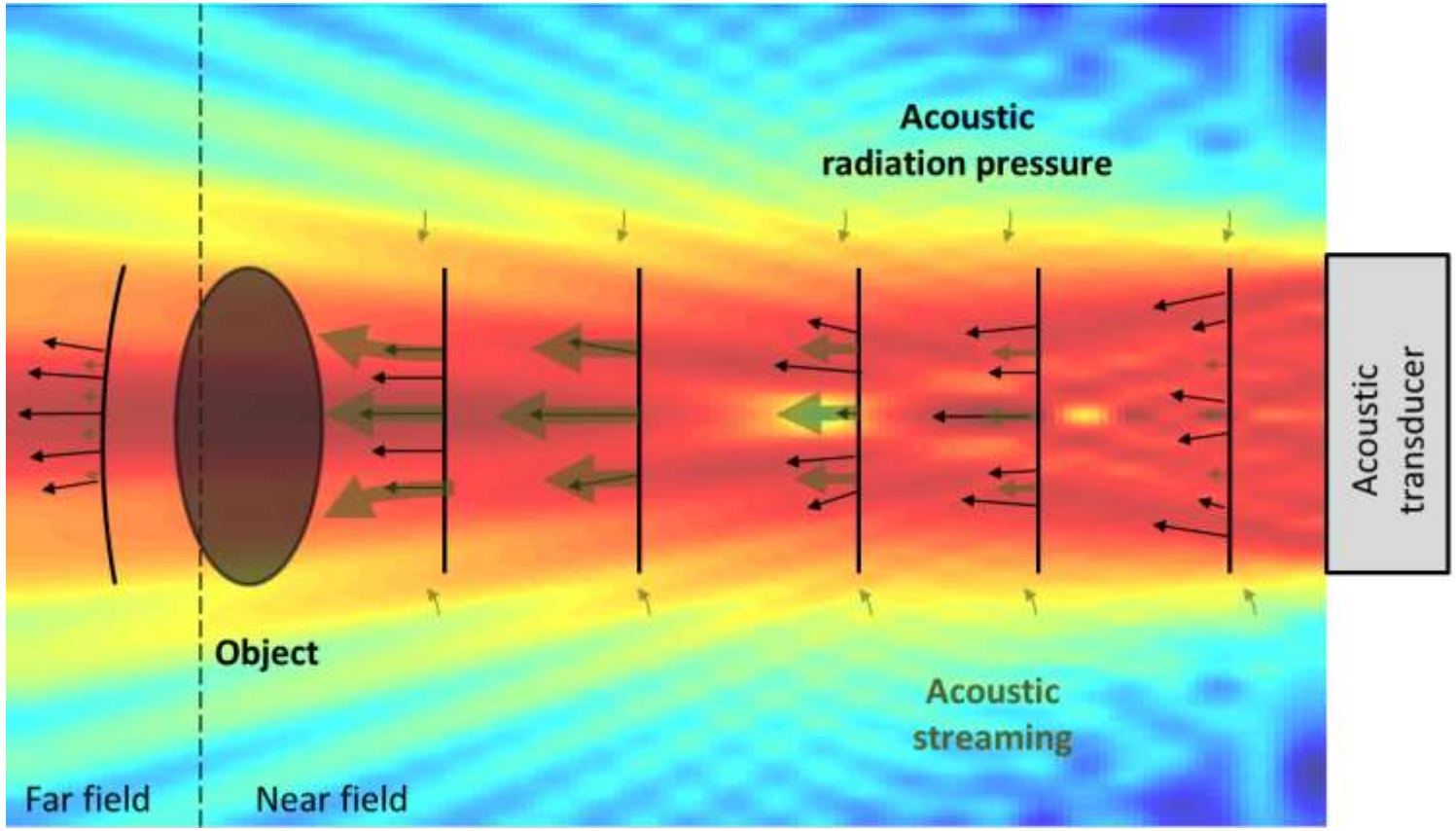
$$100\ \text{Hz} \leq \mathbf{PRF} \leq 1\ \text{KHz}$$

Most common LIPUS protocol

Exogen's Sonic Accelerated Fracture Healing System (SAFHS) (Exogen, Inc, Piscataway, NJ)

Transducer	round, unfocused
Frequency	f = 1.5 MHz
Pulse Repetition Frequency	PRF=1 kHz
Duty Cycle	DC 20% (200 µs ON, 800 µs OFF)
Intensity	I_{SATA}=30 mW/cm²
Duration	1 x 20 min /day for up to several months

Mechanical effects introduced by a pulsed acoustic field



Ultrafast:	Oscillatory Strain at Ultrasound Frequency
Fast:	Acoustic Radiation Force at Pulse Repetition Frequency
Slow:	Acoustic Streaming

LIPUS studies…

…discussed in this talk

In vitro

Padilla et al. “Stimulation of bone repair with ultrasound: A review of the possible mechanic effects“ Ultrasonics (2014)

- 211 (mainly in-vitro) studies

In vivo (systematic reviews and meta-analyses)

Schandelmaier et al. *BMJ* (2017)

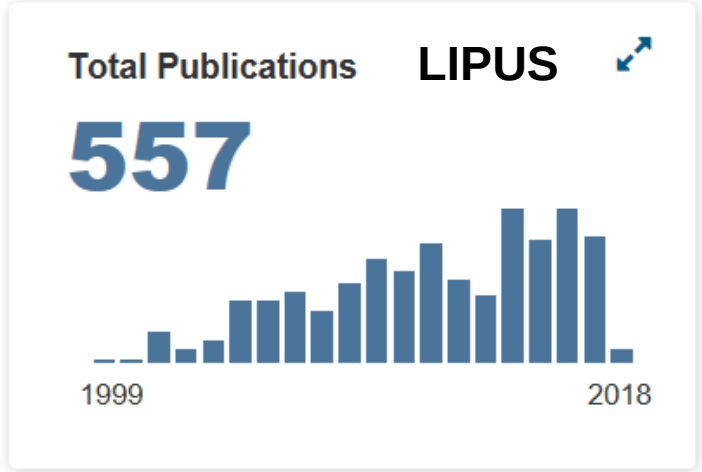
Shenghan et al. *Medicine* (2017)

Leighton et al. *Injury* (2017)

Rutten et al. *JBJS Reviews* (2016)

Padilla et al. *AdvExpMedBiol* (2016)

… for comparison



ISI Web of Science, March 2018

Intrinsic problems with the application of LIPUS

- correct **application by patient**
  - ➢ positioning, coupling

- limited **adherence to treatment**
  - ➢ inconvenient application 20min/day overs months
  - ➢ need to carry device, blocks daily activity

- sound attenuation / reflection in variable amounts of soft/callus tissues / implants
  - ➢ **acoustic dose** at fracture site?

Status quo of clinical trials on LIPUS treatment

- most randomized controlled trials **RCTs** are described for fresh fractures
- often **low number** of cases: N = 8 – 500 (TRUST study)
- "... RCTs on LIPUS treatment are poorly reported, lack outcomes important to patients, and are at high risk of bias." (Schandelmair et al., 2017)
- **almost no RCTS for delayed- and non-unions**
- most of the clinical studies are funded by the producer/manufacturer
  - *"… only 12% (3/26) of trials were free from industry funding" (Schandelmair et. al., 2017)*

Intrinsic challenge of clinical LIPUS trials for nonunions

- when a non-union is established, surgery is a first-line treatment.
- LIPUS is advised only if all the procedures failed / too risky.

No Data: **1st surgery vs LIPUS**

revision surgery vs LIPUS

- surgeons are reluctant to undertake an RCT treating nonunion without surgery
- Institutional Review Boards may be reluctant to approve such RCTs
- patient recruitment for an operative vs non-operative treatment protocol is difficult (Leighton et al., 2017)

➢ there is currently **no way to evaluate the „perfect time“** to initiate LIPUS treatment

Status quo of systematic reviews and meta-analyses on LIPUS treatment

	Trials	Cases		
Schandelmaier et al. *BMJ* (2017)	26 RCTs	1594 min: 8 max: 501	LIPUS vs sham or no device **any kind of fracture / osteotomy**	• **all trials** ➢ reduction to full load bearing, pain, radiographic healing • **4 trials with low risk of bias** ➢ no LIPUS effect ➢ **moderate quality evidence that LIPUS has no effect**
Lou et al. *Medicine* (2017)	12 RCTs	1099	LIPUS vs sham or no device **fresh fractures**	➢ reduction of time to fracture union ➢ improved quality of life ➢ **No effects on time to work and full weight bearing, and incidence rate of delayed or nonunions**
Leighton et al. *Injury* (2017)	13 **N**RCTs	1441	LIPUS vs sham or no device **nonunions**	➢ LIPUS effect size 82-84% ➢ hypertrophic > atrophic ➢ <6 months from surgery favorable
Rutten et al. *JBJS Reviews* (2016)	24 RCTs	429	LIPUS vs sham or no device **any type of fracture, delayed union, nonunion**	➢ Reduced healing time (39.8 days) ➢ 3 RCTs: no effect for return to work • 2 HQ RCTs: ➢ **Enhanced bone formation in delayed/impaired cases** ➢ **No prevention of delayed or nonunions**

Status quo: Schandelmaier et al. *BMJ* (2017)

Low quality evidence from (26 trials):

- possible reduction of days to full weight bearing, pain
- large reduction in time to radiographic healing
  - No effects for subgroups (only analyzed for radiographic healing) (*management type / stress fractures / nonunion / osteotomy*)

Moderate quality evidence:

- no effect on time to return to work or the number of subsequent operations
- no effect on days to radiographic healing

High quality evidence (4 trials, <u>only fresh fractures</u>):

- no effect on pain reduction, days to full weight bearing, or adverse effects related to the device

Status quo: Fresh fractures only Schandelmaier et al. *BMJ* (2017)

- **Strong recommendation against LIPUS**

Included	**LIPUS/Sham**	**Mean Age**	**Type**	**Primary Management**
Busse, 2014	(23/28)	40	Fresh Fracture	Operative
Busse, 2016	(250/251)	40	Fresh Fracture	Operative
Emani, 1999	(15/17)	37	Fresh Fracture	Operative
Lubbert, 2008	(61/59)	38	Fresh Fracture	Non-operative
Excluded				
Heckmann, 1994	(48/49)	33	Fresh Fracture	Non-Operative
Kristiansen, 1997	(40/45)	**56**	Fresh Fracture	Non-Operative

is based on 4 „low risk“ studies (N = 349/355) including

- **young population**
- **primary treatment with lowest complication rate (reamed nails)**

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Status quo: Fresh Fractures Lou et al. *Medicine* (2017)

Moderate to high-quality evidence (12 RCTs):

- reduces the time to fracture union
- improves the quality of life (SF-36)

- does not affect functional recovery (time to return to work / full weight bearing)
- does not reduce incidence rate of delayed union and nonunion.

Recommendations: LIPUS may be better for …

- fractures with conservative treatment than those with operative treatment.
- upper limb fractures than lower limb fractures

LIPUS may not necessarily reduce the incident rate of delayed union and nonunion.

Status quo: Nonunions Leighton et al. *Injury* (2017)

Low to moderate quality evidence (MINORS score for NRCTS):

- LIPUS effect size 82-84%
- effect larger in hypertrophic than in biologically inactive atrophic nonunions
- <6 months from surgery favorable

Recommendations

LIPUS can heal without concurrent surgery (but RCTs are needed for confirmation)

LIPUS should be used for nonunions

- as alternative rather than an adjuvant to surgery, if
  - LIPUS treatment starts immediately after the diagnosis of the nonunion
  - the nonunion is biologically active
  - surgery is high risk

Summary of factors that influence LIPUS outcome

Fixation type

- Higher failure rate for non-unions stabilized by intramedullary nail in comparison to plate & screw and external fixator (Watanabe et al., 2013, Lou et al. 2017)

➢ **Due to intrinsic failure rate difference or interaction of sound wave with implant?**

Amount of soft tissue

- "*Success rates of delayed unions were lower for deeper bones like the femur and humerus than for subcutaneous bones like the tibia/tibia–fibula and radius/radius–ulna.*“ (Mayr et al., 2000)

➢ **We need a target „acoustic dose“ instead of instrument output values!**

Biological competence

- Hypertrophic non-unions (biologically active) benefit more form LIPUS treatment than atrophic ones (Leighton et al., 2017)

➢ **LIPUS cannot bypass biological component of bone regeneration**

Additional co-factors that affect LIPUS outcome

Age, sex, and risk factors (e.g., smoking) can significantly influence bone healing

- "Larger differences between LIPUS and control groups were noted for females (50%), older patients (45%), distal fractures (41%), oblique fractures (46%), larger fractures (45%), and absence of fibular fractures (58%)...“ (Watanabe et al., 2010)

- Patient age was associated with failure to heal among chronic nonunions (Zura et al. 2015)

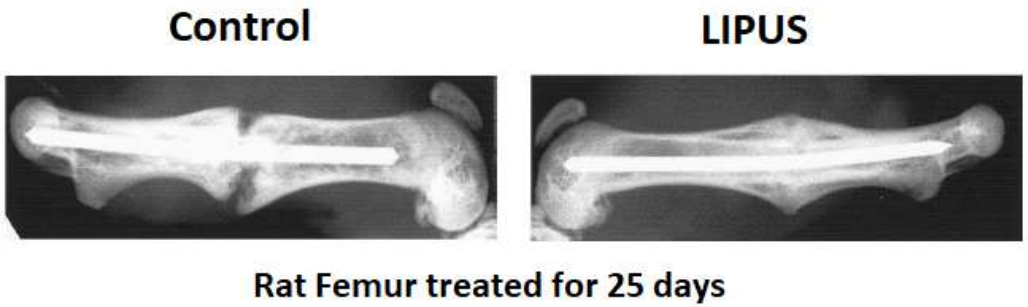
➢ **Is current LIPUS protocol optimal for all cases?**

In-vivo studies in animals

LIPUS enhances bone regeneration

- Proven across different species: rat, rabbit, dog, sheep

a) Radiographically



(Azuma et al., 2001)

b) Histologically

(Hasuike et al., 2011)

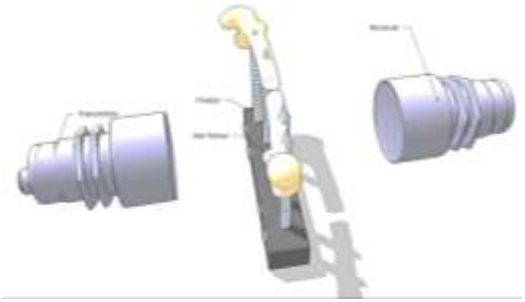
c) Biochemically & **d) via Mechanical Testing**

- Effects observed at **each stage of bone healing *in vivo*** in rat femur fracture (Azuma et. al., 2001)
- However, **lack of mechanistic studies** (i.e., targeting bio-physical mechanisms)

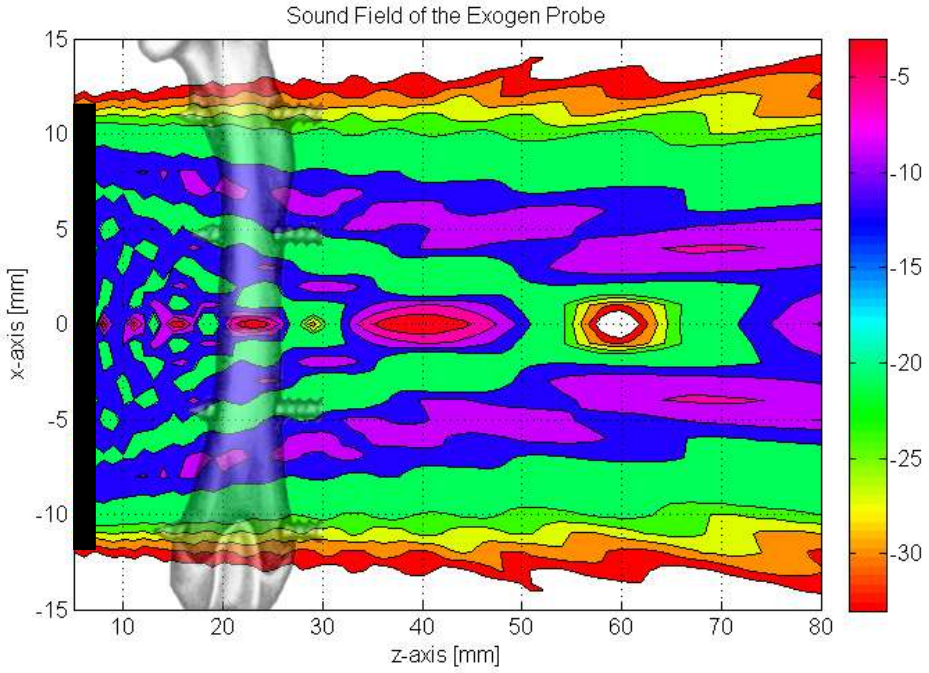
➢ Challenge: **Animal vs Transducer** size

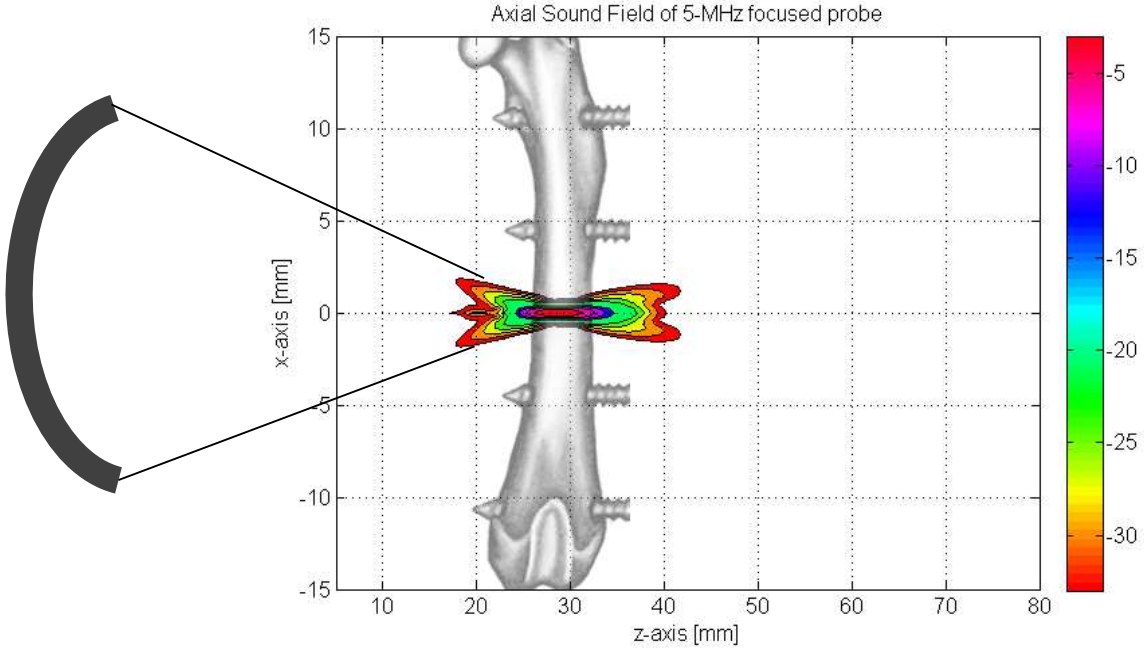
Problem of LIPUS stimulation in small animals

Exogen's Sonic Accelerated Fracture Healing System (SAFHS) (Exogen, Inc, Piscataway, NJ)



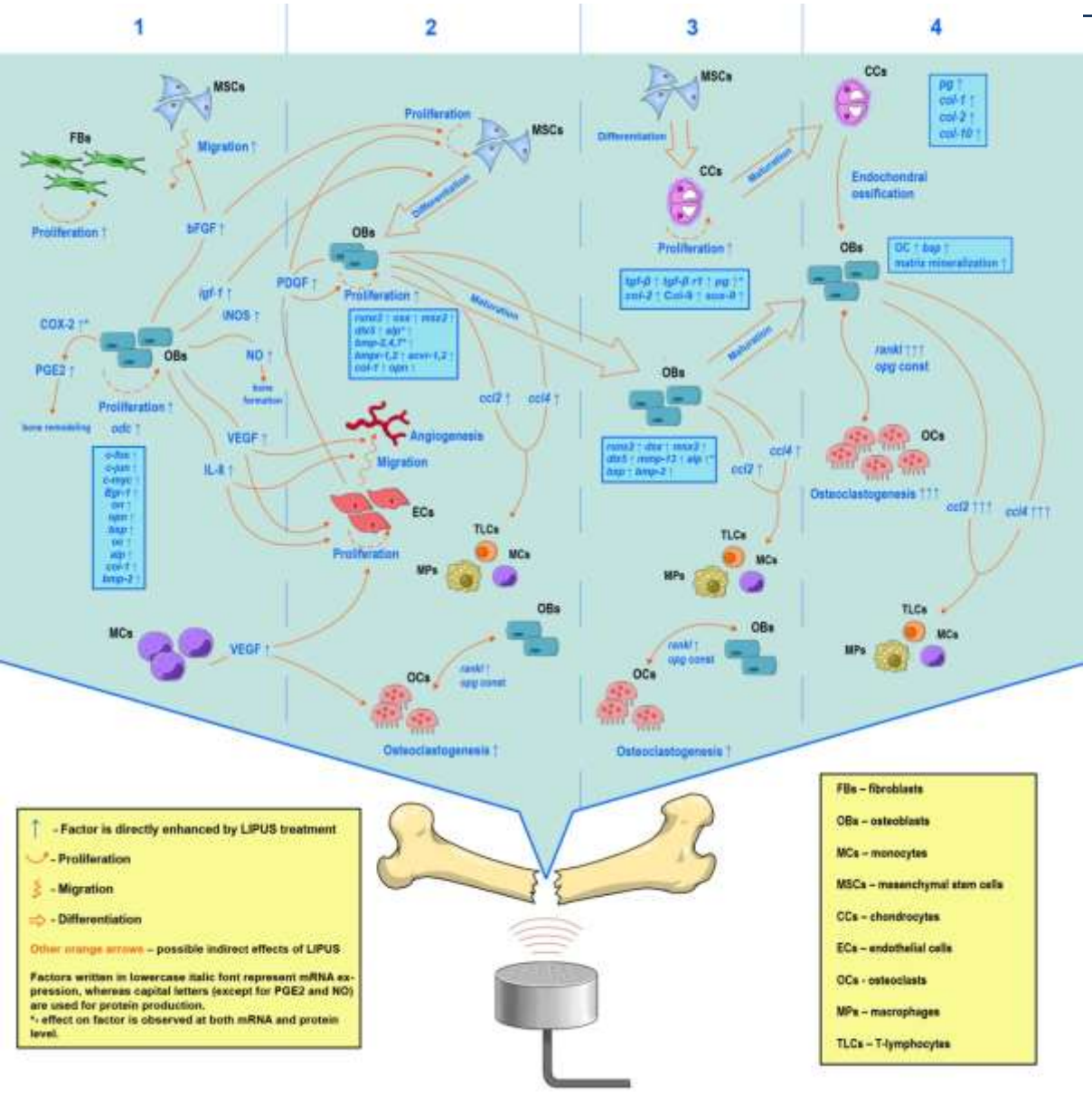
Charité Focused Imaging & Stimulation System (Berlin, Germany)





In-vitro cell stimulation studies

Summary of *in-vitro* findings



Padilla and Puts *et al*., 2014

- ***In-vitro*** studies suggest favorable impact of LIPUS during all phases of bone healing

- However, often studies report controversial effects (e.g., proliferation and differentiation of osteoprogenitors)

Inconsistency could be caused by

- Physical artefacts in Set-Ups (standing waves, heating,…)
- Species dependent effects
- Cell-origin (site) specificity
- LIPUS parameters

- **Effects induced by *in-vitro* artefacts may not occur *in vivo***

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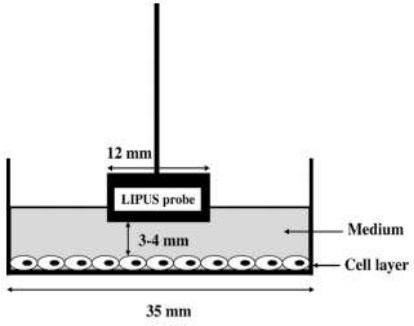
Most common LIPUS protocol

Transducer	round, unfocused
Frequency	f = 1.5 MHz
Pulse Repetition Frequency	PRF=1 kHz
Duty Cycle	DC 20% (200 µs ON, 800 µs OFF)
Intensity	I_{SATA}=30 mW/cm²
Duration	1 x 20 min /day for up to several months

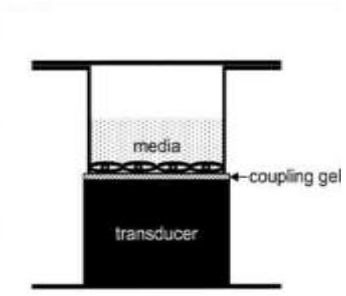
In Vivo

FDA approved Exogen's Sonic Accelerated Fracture Healing System (SAFHS) (Exogen, Inc, Piscataway, NJ)

In Vitro



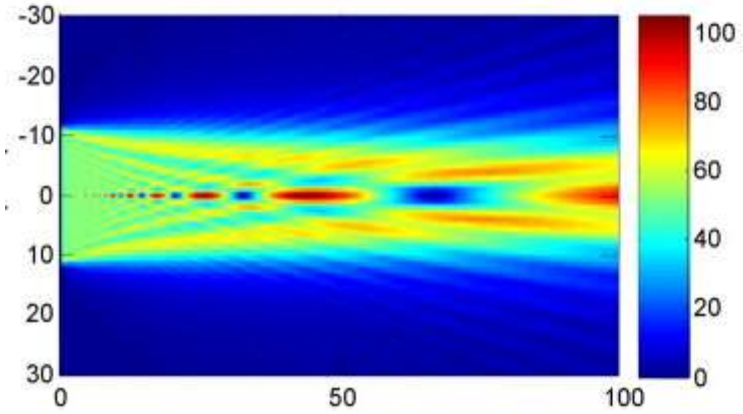
Ikeda *et al*., 2006



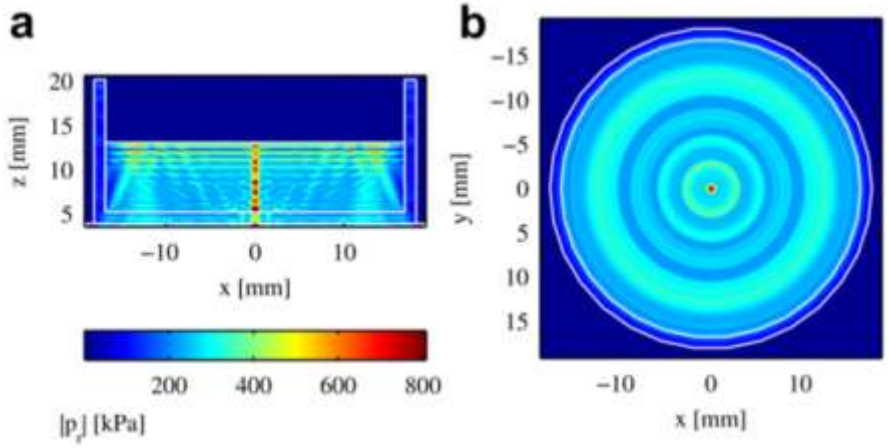
Sena *et al*., 2005

Problems with common in-vitro setups

Near Field Interference

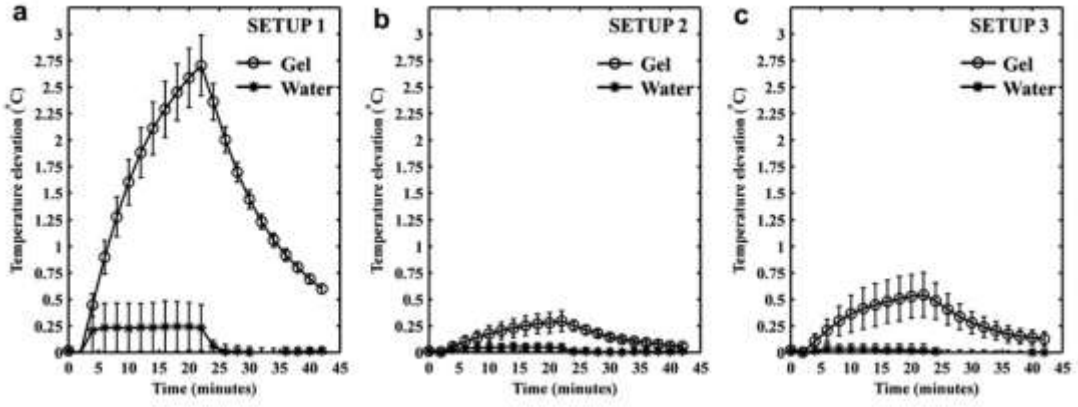


Ring Interference and Standing waves



Hensel *et al.*, 2011

Temperature elevation for various LIPUS setups

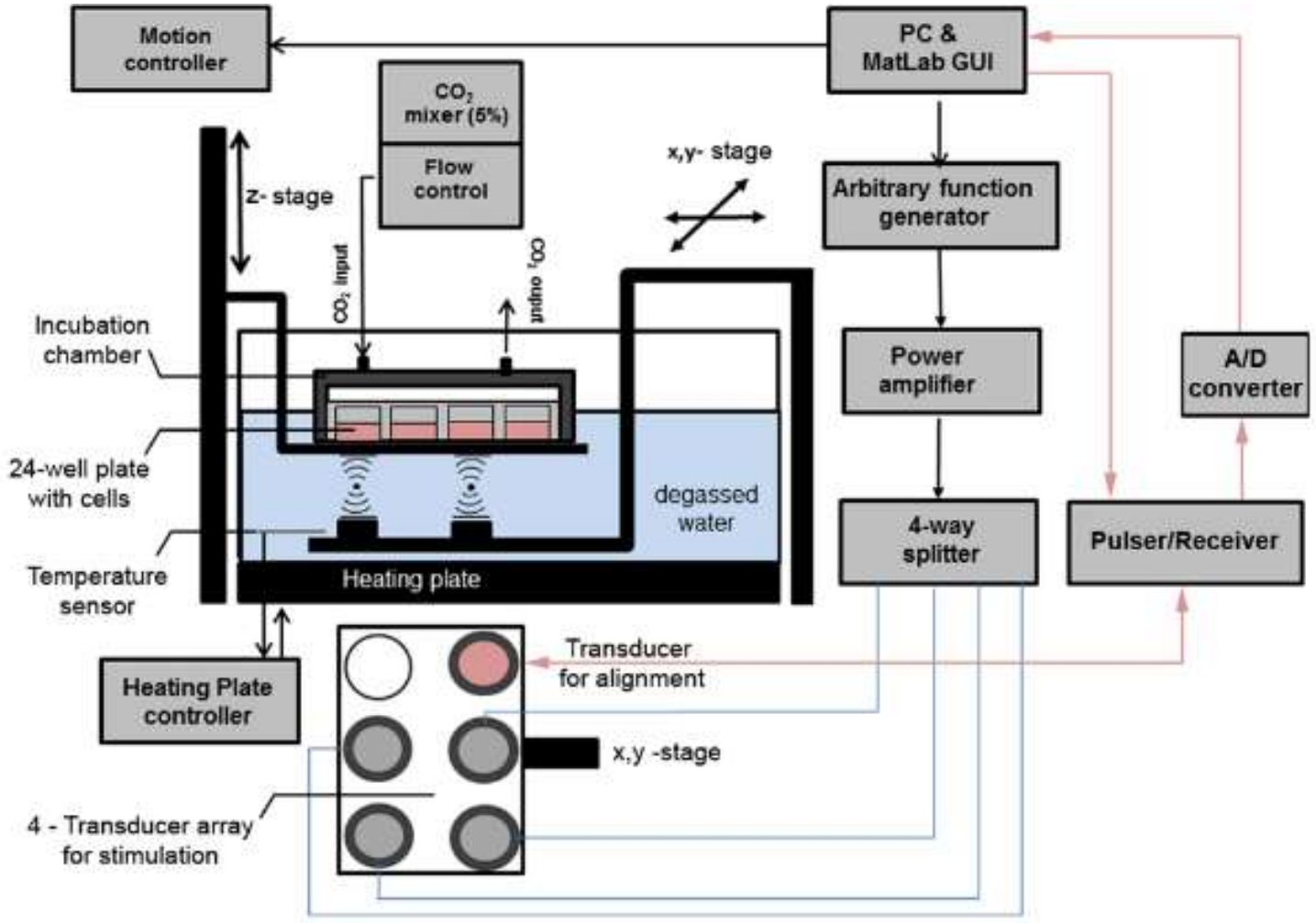


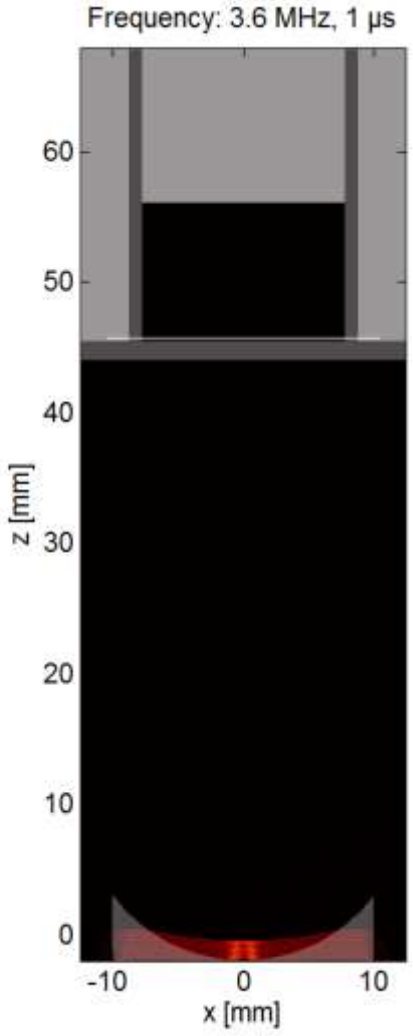
Leskinen & Hynynen, 2012

→ **Reported effects & intensity level are usually not those experienced by cells.**

Alternative – Focused LIPUS

FLIPUS Cell Culture Stimulation Setup





Puts et al. IEEE TUFFC (2016)

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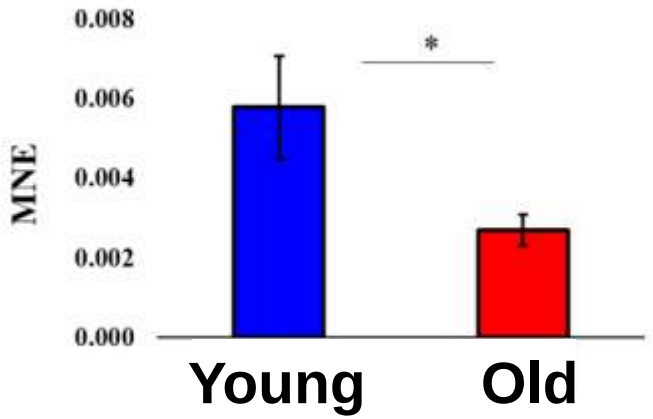
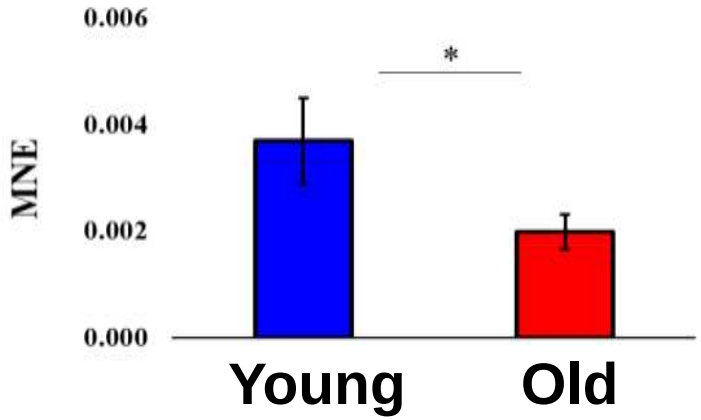
Age-dependent differences upon LIPUS exposure *in vitro*

Osteocalcin



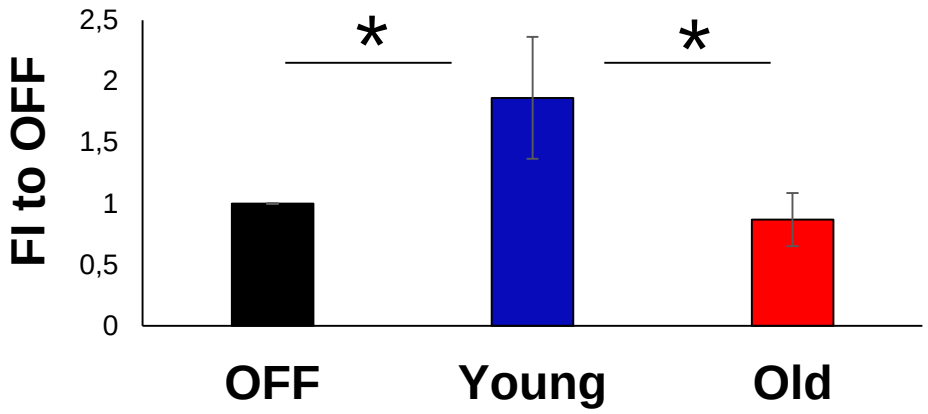
Drop in Osteogenic Potential of MSCs with Age

RUNX2



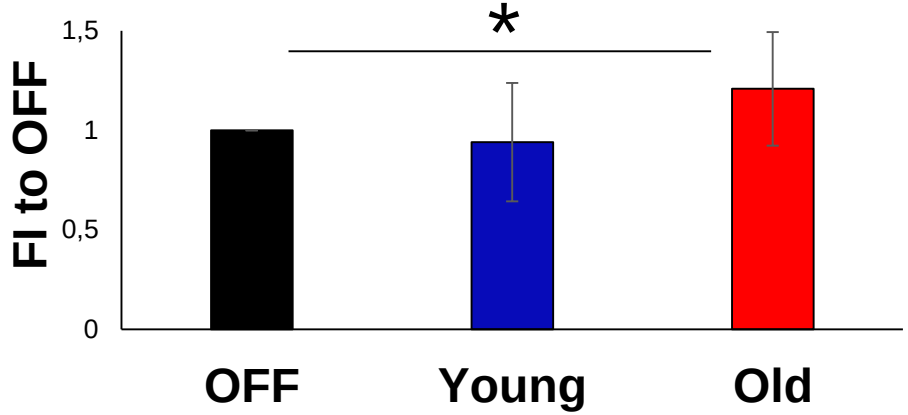
In **young rMSCs,** osteogenic differentiation **enhanced** when low **LIPUS** dose (**11.7 mW/cm²**), whereas **in old rMSCs** when high dose (**44.5 mW/cm²**) applied

Osteocalcin 11.7 mW/cm²



n = 9, *p < 0.05

RUNX2 44.5 mW/cm²



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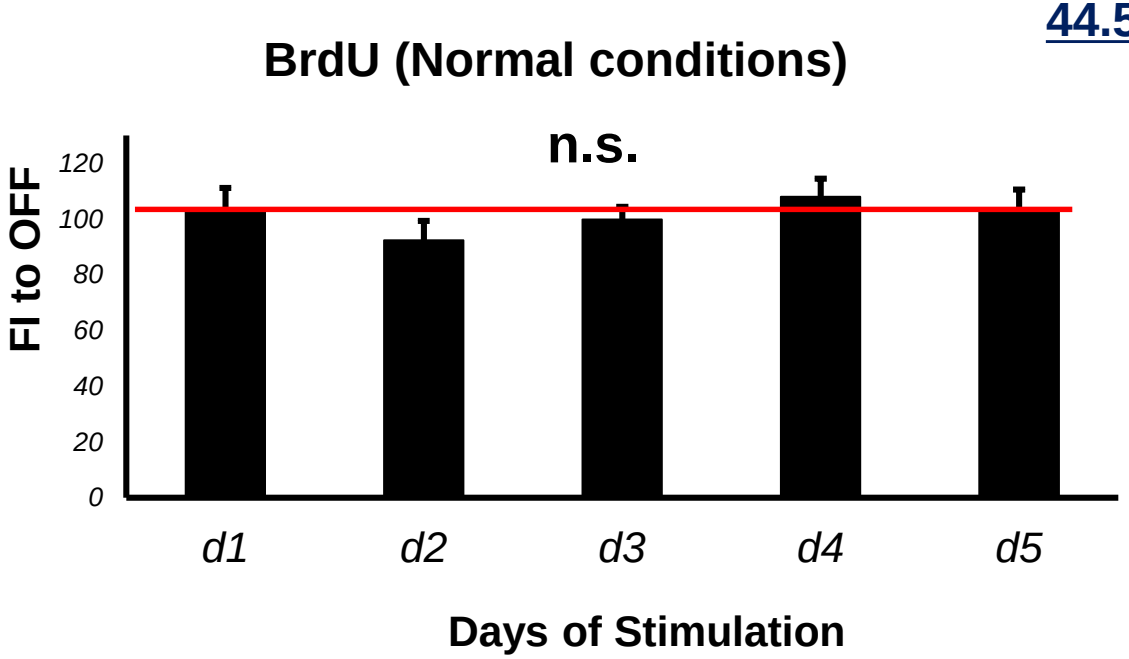
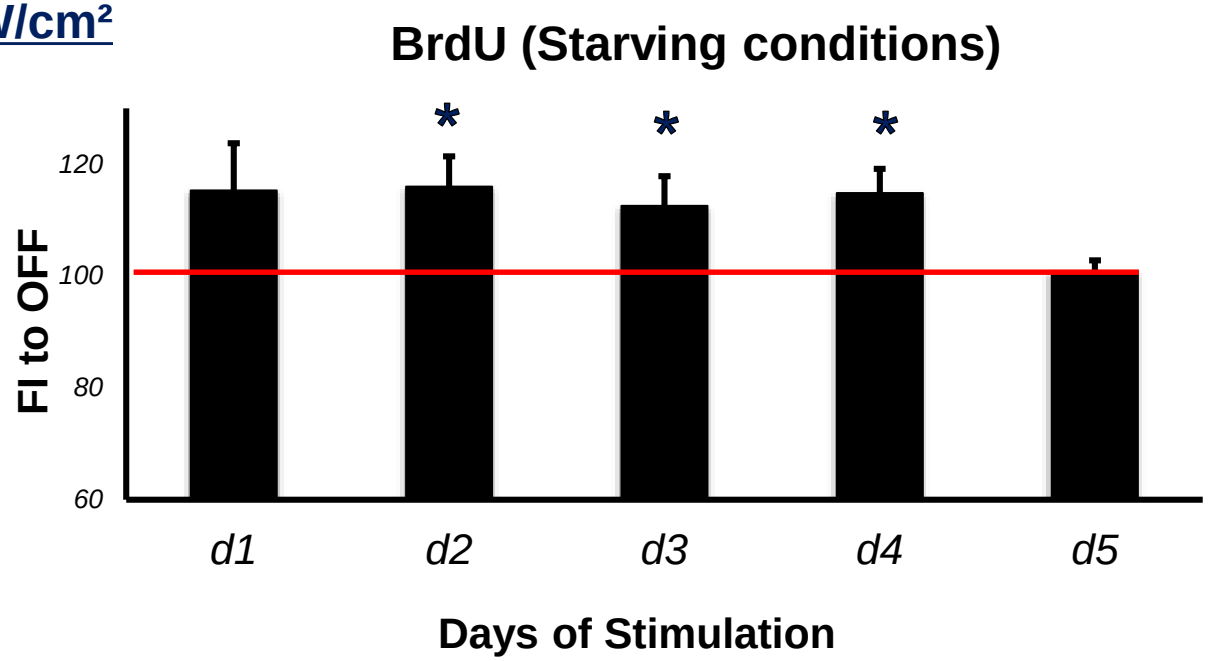
Puts *et al*., 2016, UMB

Effects under Compromized Physiological Conditions *in vitro*

44.5 mW/cm²





n = 3, *p < 0.05

- **Proliferation** of murine MC3T3-E1 preosteoblasts is **enhanced after FLIPUS** treatment when cells are in **Starving (2% FCS)** medium conditions
- Similar results observed for **rat MSCs**

Puts *et al*., 2014, IEEE International Ultrasonics Proceedings

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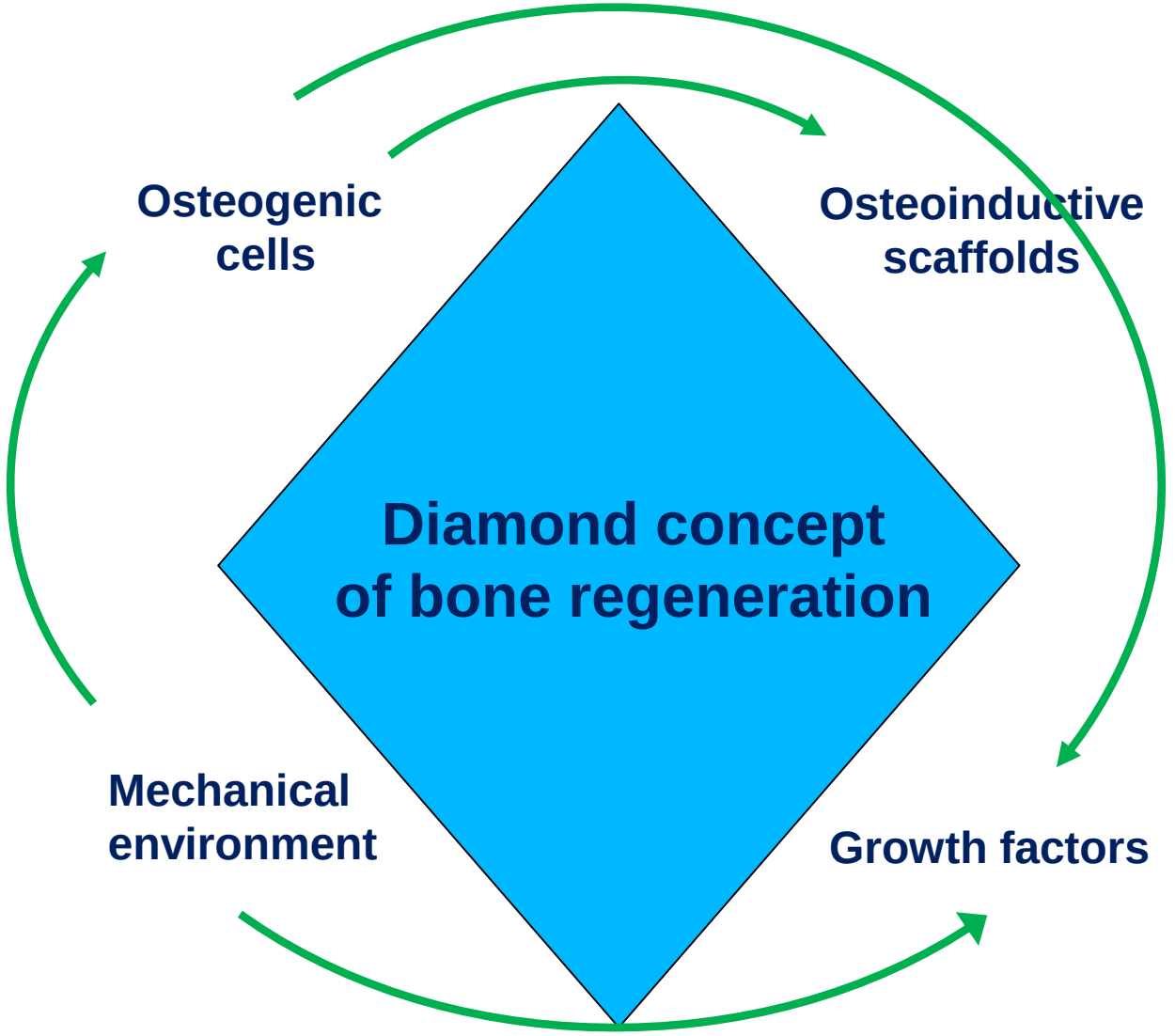
Summary

LIPUS **supports endogenous regeneration** from the mechanical side

The effect of LIPUS is limited if:

- **All conditions are already very good**
- **handshake between mechanical, biological, structural and biochemical environments is compromised**



Conclusions

Basic Science Level

- mechanisms of action, optimal acoustic dose and influencing factors are on the way to be established using improved technology
- establish target dose measures

Translation to Clinical Application

- identify cases, for which LIPUS may / may not have an effect
- identify case and patient specific acoustic doses
- improve technology (e.g. wearable focused array technology)
- combine LIPUS with biological (cell) and chemical (growth factors) treatments

Conclusions

Clinical Studies

- more large scale high-quality "… studies are needed to determine the **clinical circumstances** under which LIPUS is truly valid and to **examine the optimal approach** for the use of this adjunctive therapy." (Lou et al. 2017)
- these studies should…
  - target specific cases
  - assess multiple outcome parameters, including patient benefits
  - assess cost-effectiveness

➢ **Our current level of evidence is still positive, but sparse and weak**