Degradable implants based on magnesium – what do we need for translation into clinics?

Frank Feyerabend

12.05.2014 / Smolenice Castle, Slovakia

Helmholtz-Zentrum Geesthacht
Zentrum für Material- und Küstenforschung

Introduction

1st reference on the use of magnesium implants

or stasis which *cold* combined with elastic and equable pressure produce.

EDWARD C. HUSE, M. D.

ROCKFORD, ILLS., June 24th, 1878.

(We are pleased to publish the practical communication of our correspondent, but must advise him that his method of procedure has been given to the public by an earlier writer.—ED.)

A New Ligature.

ch Prof. Lister has introduced to the profession, are of great advantage over the time-honored silken ones, or those formed from silver wire. Torsion, acupuncture and the various devices in vogue from time to time, have each had their friends and enemies, their advantages and disadvantages. The principal danger in using any and all ligatures especially upon vessels of the first magnitude, such as the subclavian, the carotid, or the iliac, is secondary hæmorrhage. Septicæmia is not likely to occur after using carbolized ligatures, yet the chief objection to them is that the material of which they are composed is organic. Hence, like all organic substances, they are liable to be either imperfect in structure and break, to be imperfectly carbolized and hence rot, or to produce irritant and septic effects at the point of application. It is not easy to see how the multiple conditions on which their absorption depends, can, in every instance, be complied with, especially outside the walls of a hospital. At best and in any event, the life of a patient, where one of these ligatures has been used, hangs upon little more than a thread and often far less than that. A ligature, to be perfect of its kind, should possess the elements of strength, ease of application, readiness of absorption and simplicity. It should not depend for its advantages upon a material perishable in its nature under *ordinary* circumstances, neither should its perishability and consequent absorption on which its whole value depends, be left to accident or chance.

There is but one substance in nature which entirely meets and fulfills the requisit
writer has carefully
submit his plan un

If a piece of magnesium wire

magnesia. The ash which burning magnesium forms, is ordinary magnesia, plain and simple. It is thus innocuous and readily absorbed.

Its action upon the animal economy is absolutely harmless to all textures everywhere. When an artery or vein is tied with a loop of magnesium wire, this process of oxidation goes on more slowly in the presence of animal heat and moisture, yet none the less surely, none the less completely than when it is burned up in the way above cited.

will be absorbed beyond a peradventure in all instances. Thus far I have used it but three times, once upon the radial artery and twice in the operation for varicocele. It has seemed to me that

will be absorbed beyond a peradventure in all instances. Thus far I have used it but three times, once upon the radial artery and twice in the operation for varicocele. It has seemed to me that this ligature will be of a special value in ovariotomy, where it is desirable to tie the vessels of the pedicle and return it into the abdomen, and in operations for hemorrhoids. It can be used everywhere under all conceivable circumstances and contingencies; it will never break; it is always ready; it cannot untwist like cat-gut or silk; it can neither slip, become stiff or rotten; it can never provoke irritation, absorb moisture, disappoint or cause anxiety, but will always act, "*tuto cito et jucunde.*"

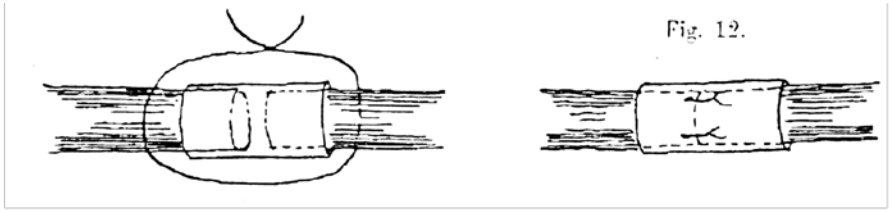
It seems to me, finally, that it must supersede all ligatures, because it is not only better, safer, more convenient and needful, but the *only* thing necessary to overcome the whole category of objections on either one of which, lives of priceless value have in hosts of cases been dependent.

I would earnestly beg that this discovery may receive careful

EDWARD C. HUSE, M. D.

ROCKFORD, ILLS., June 17th, 1878.

Introduction



1900

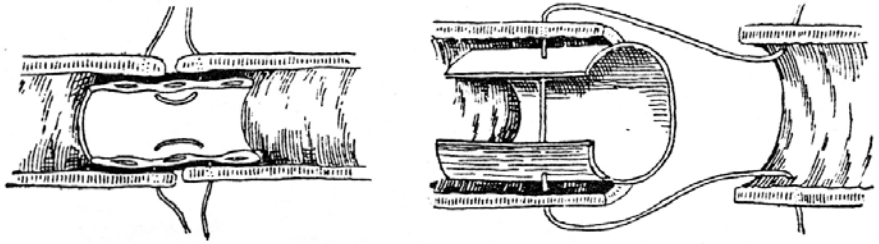
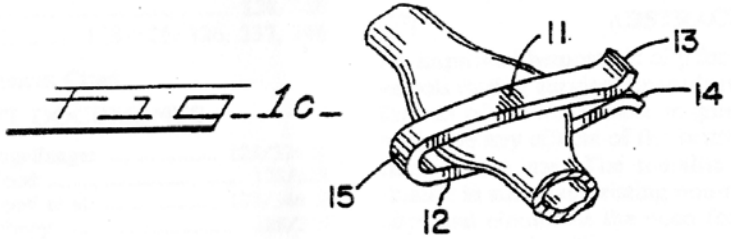
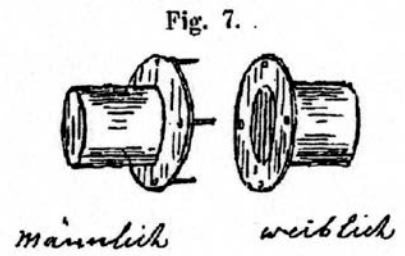


Fig. 3. Fig. 4.

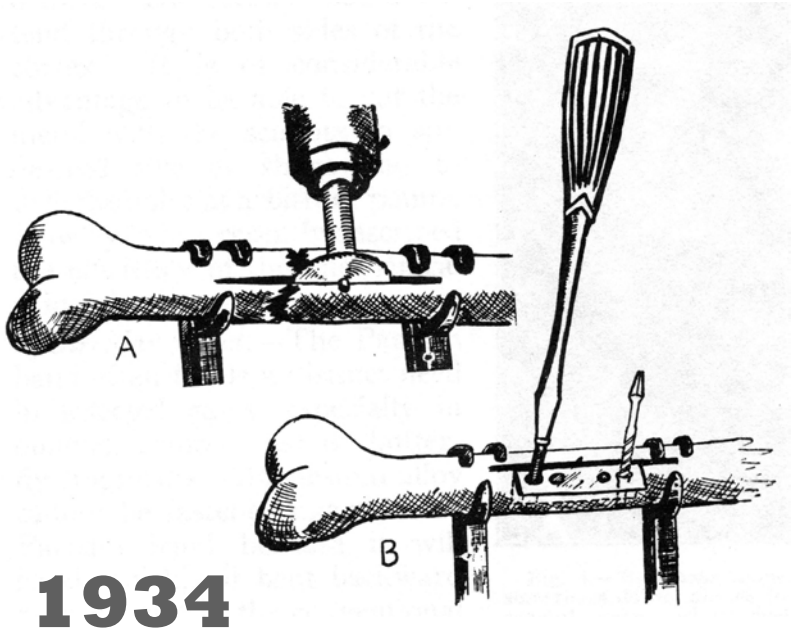
1901



1986



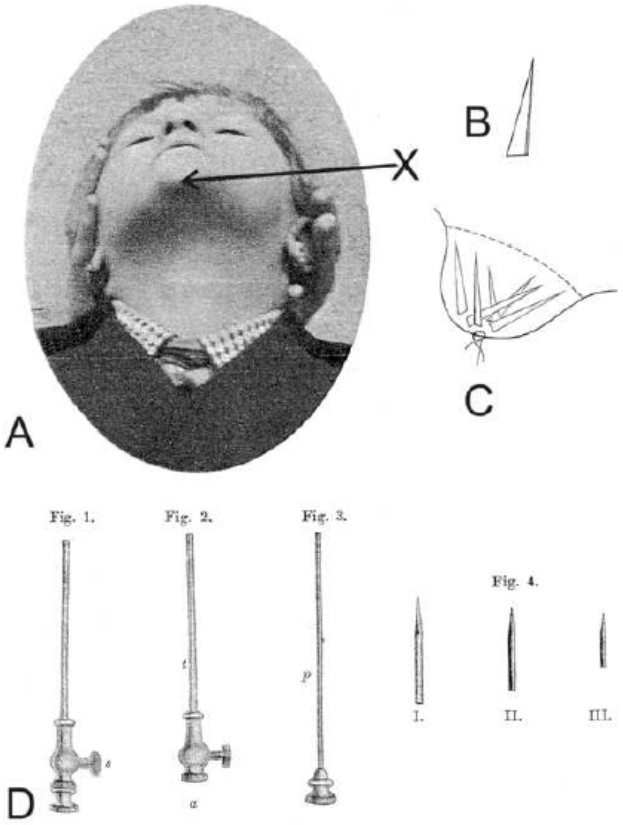
1901



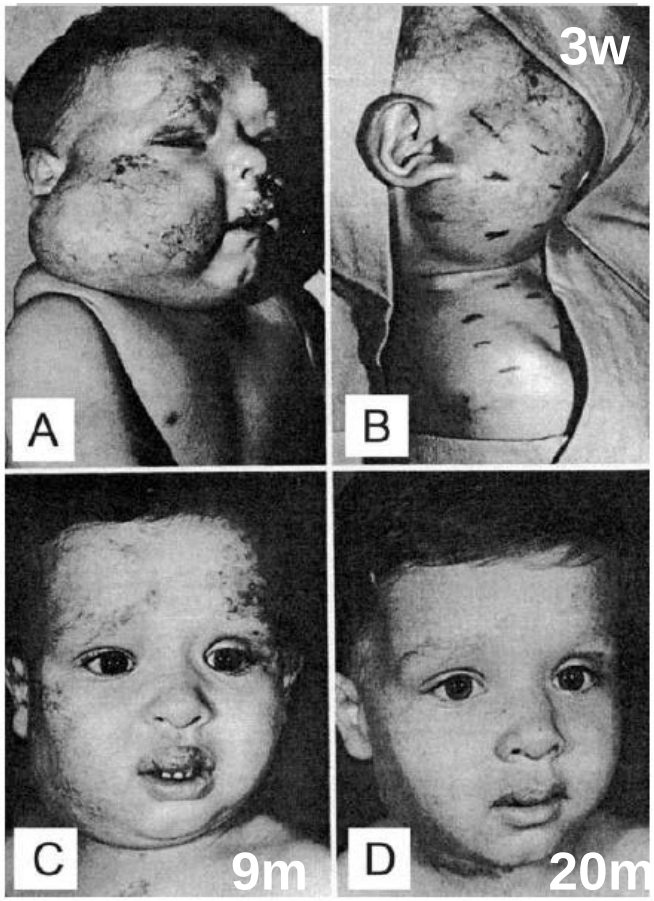
1934

Introduction

Human cavernous hemangioma treatment



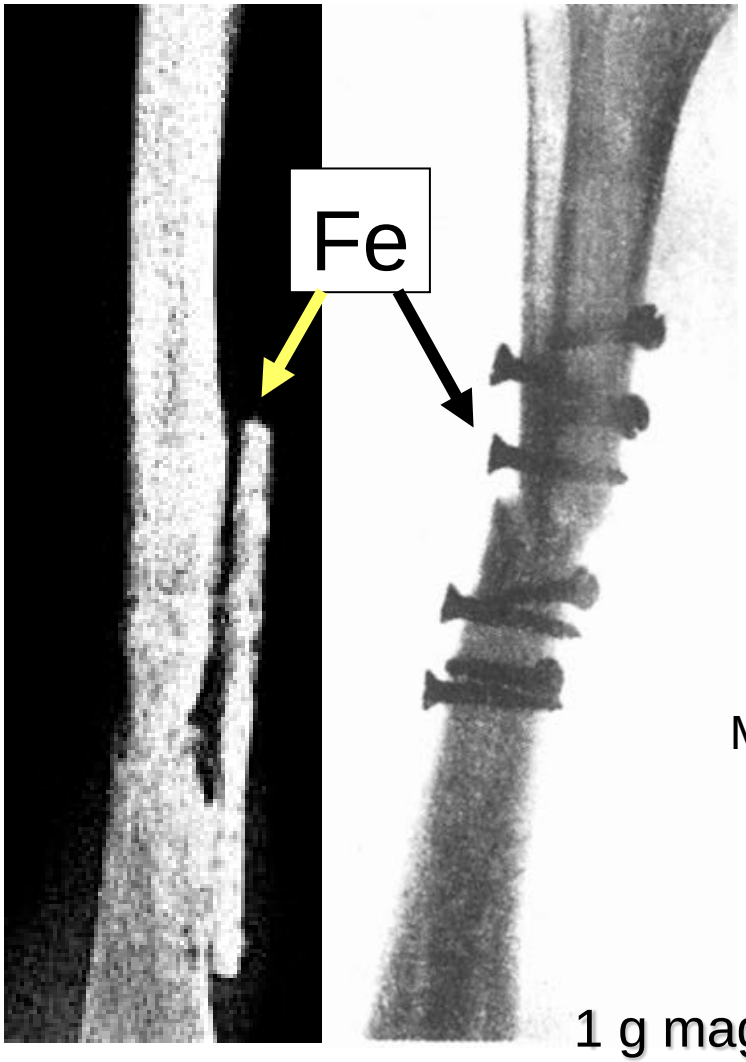
Payr E.: Zur Technik der Behandlung kavernöser Tumoren. Zentralblatt für Chirurgie **1903**;30:233-34.



Wilflingseder P, Martin R, Papp C. Magnesium seeds in the treatment of Lymph- and Haemangiomata. Chir Plastica **1981**;6:105-16.

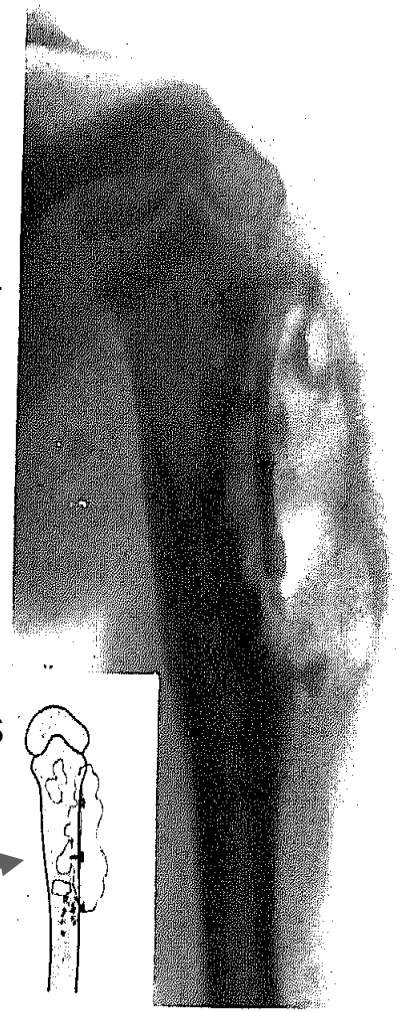
Introduction

Why are magnesium implants not standard in the clinics nowadays?



Orthopaedic Surgery

Lambotte 1906: Plate + Screws
Maier 1924: Rods, Sheets
Verbrugge 1933: Plate + Screws
McBride 1938: Plate + Screws, Rods



$$Mg + 2\,H_2O \rightarrow Mg(OH)_2 + H_2$$

1 g magnesium >> 1.08 l hydrogen gas

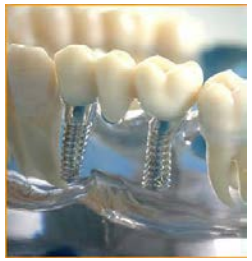
Introduction

Differences in the approval process 1900 vs. 2010

1900: Clinical application indicated by the medical doctor, ethical approval by the „Hippocratic oath“

2010: Clinical application only after approval of the local agencies (e.g. FDA, EMA, SFDA...)

medical device 93/42/EEC	ATMP EC 1394/2007	Pharmaceutical drug 2001/83/EC



Has no
- **immunological**
- **pharmacological**
- **metabolic**

effect

Mg?

Has an
- **immunological**
- **pharmacological**
- **metabolic**

effect

Slaper-Cortenbach et al. (2009)

Introduction

The translational aspect

Product:
Magnezix Compression screw 3.2
Application:
Fixation of small bone fragments
© Syntellix Ag

CE Medical *

04.09.2013: First CE-mark for an orthopaedic magnesium implant

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

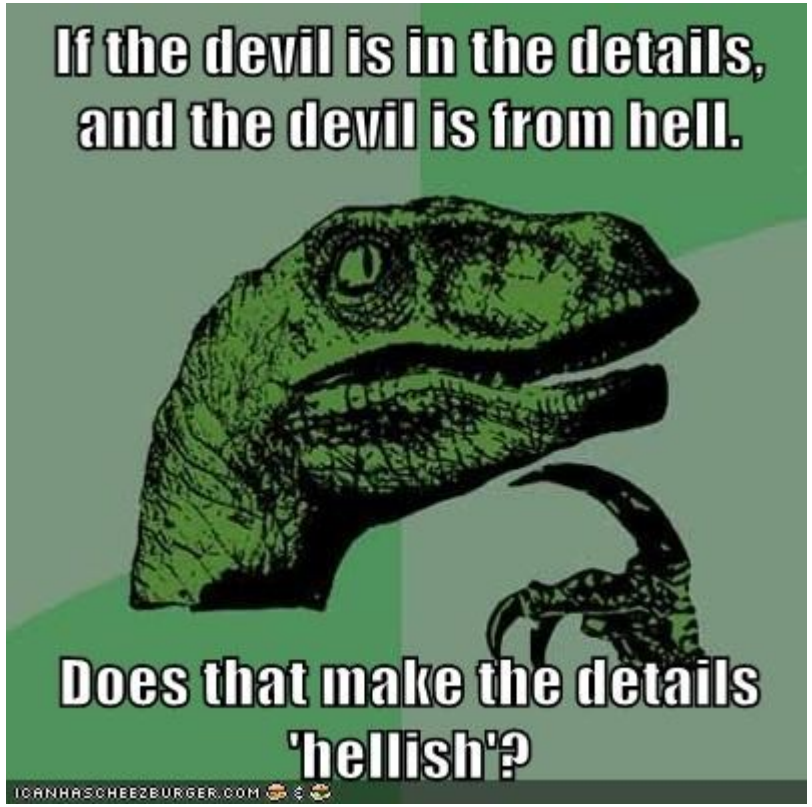
FDA

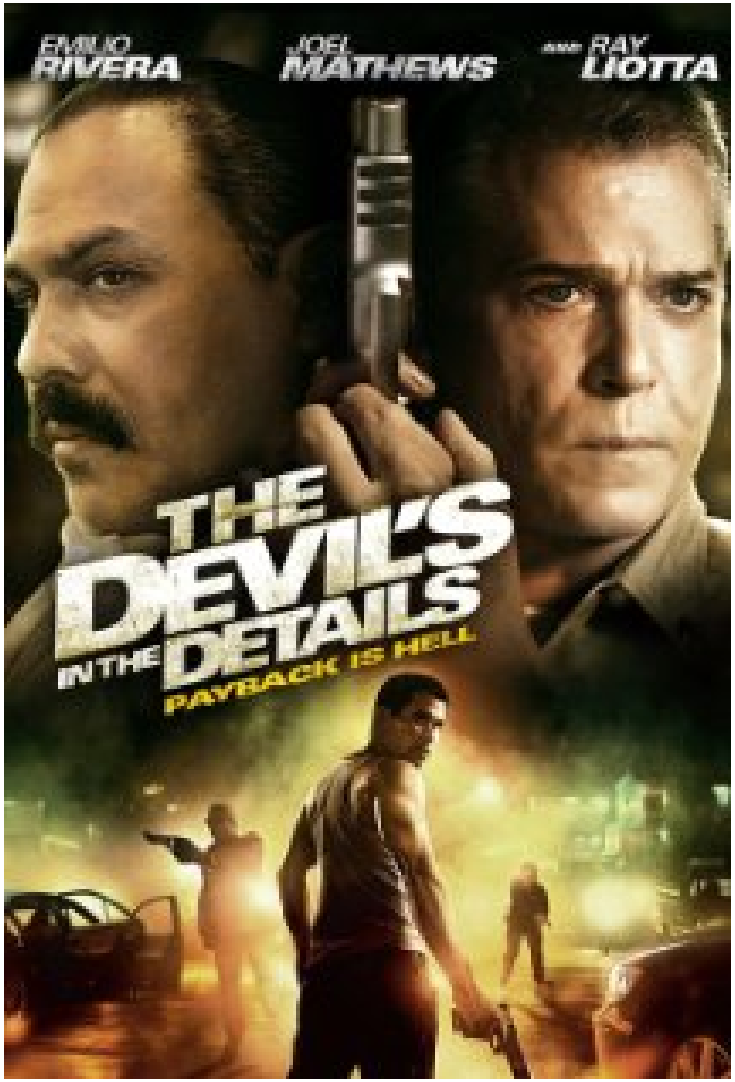
CFDA China Food and Drug Administration

* Medical Device products must be CE marked before they can be legally put into use in Europe. The products must comply with the European CE marking directives such as Medical Device Directive (MDD) 93/42/EEC or In-Vitro Diagnostic Medical Devices (IVDD) 98/79/EC and Active Implantable Medical Devices (AIMDD) 90/385/EC.
http://www.ce-mark-medical.com/

Introduction

“The devil is in the details”





Where are now the „hellish“ details?

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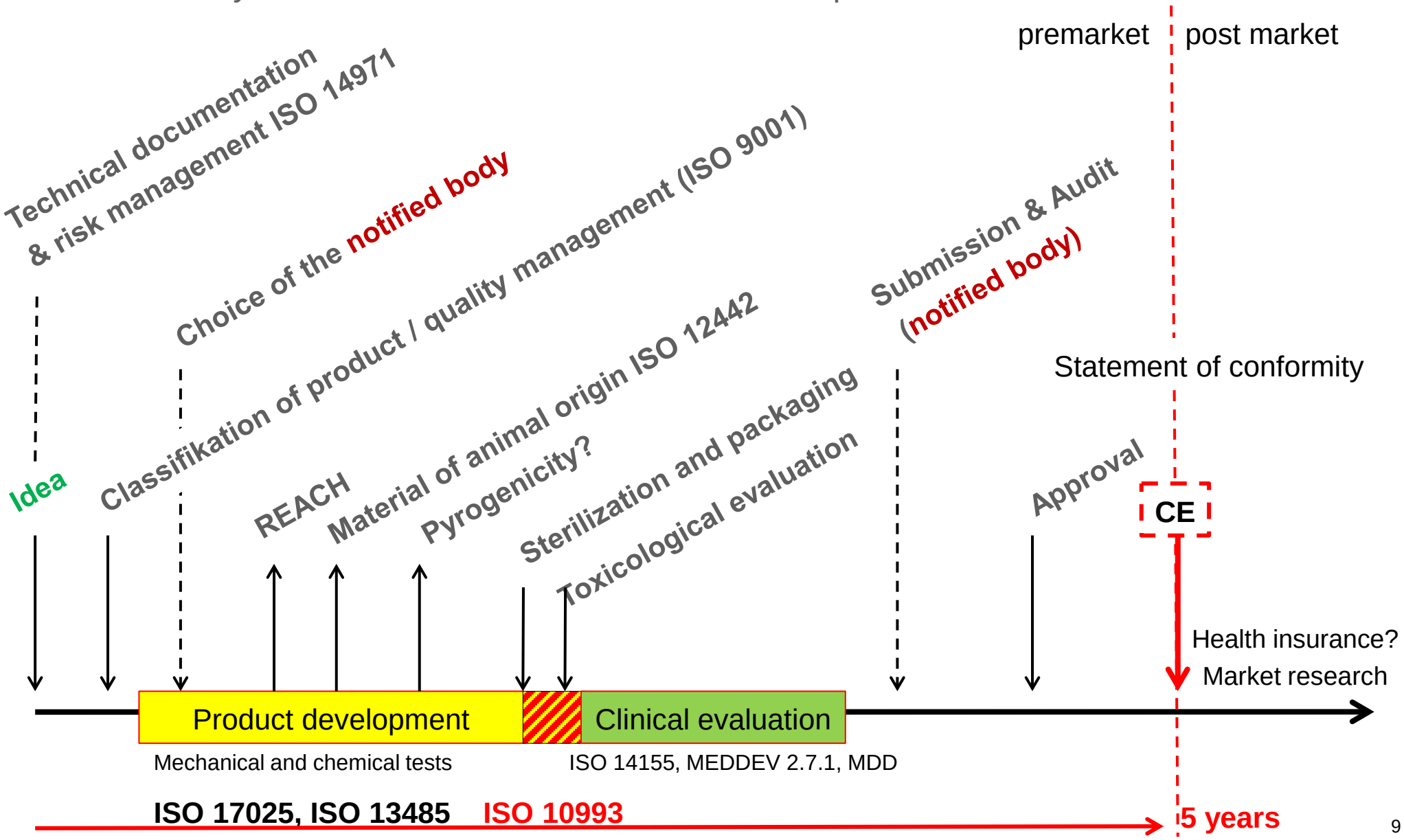
Detail 1: The way from the idea to the market for medical products



Where are now the „hellish“ details?

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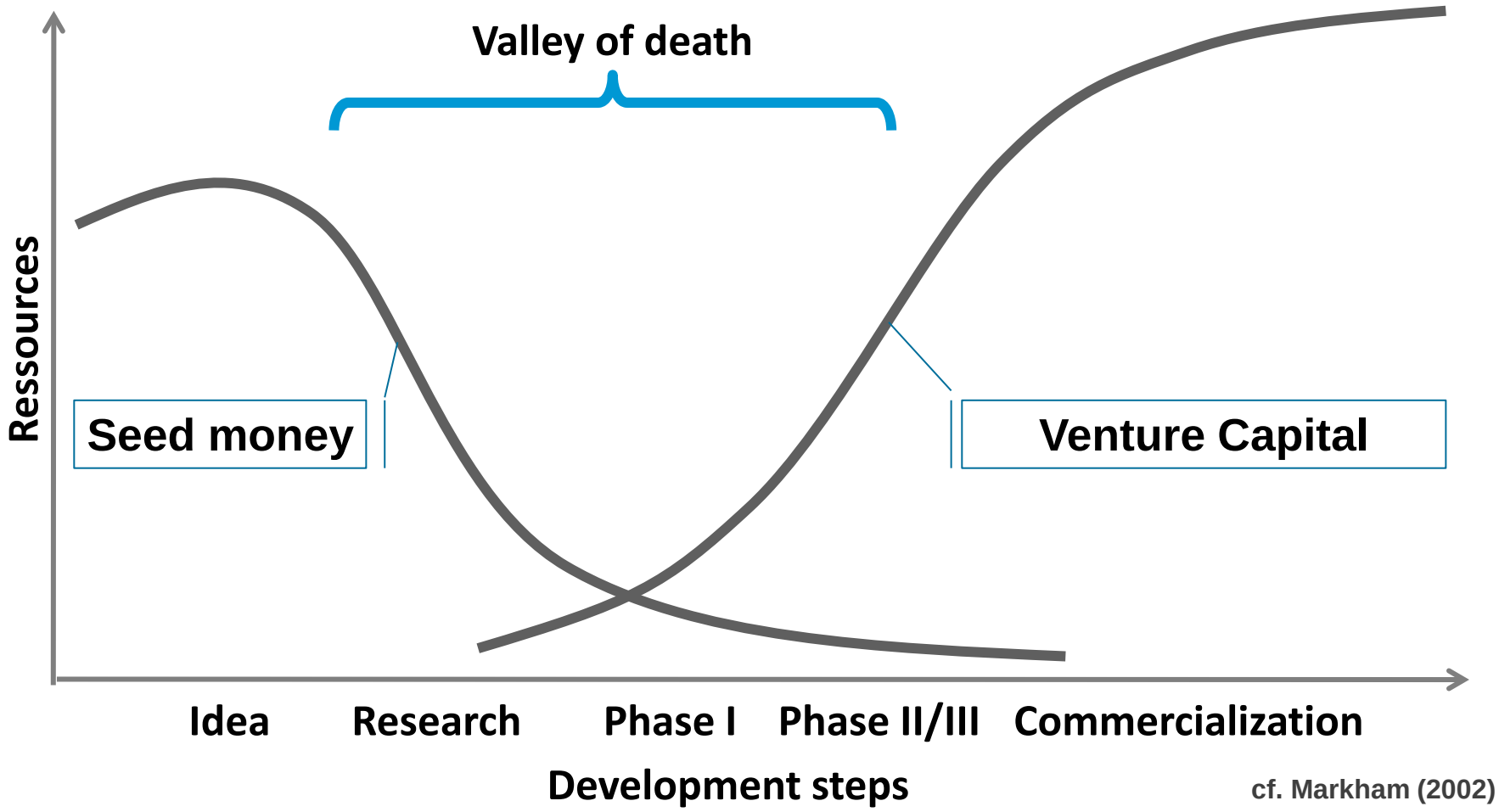
Detail 2: The money question – the „valley of death“



cf. Markham (2002)

With kind permission of Moritz Göldner, TUHH

Where are now the „hellish“ details?

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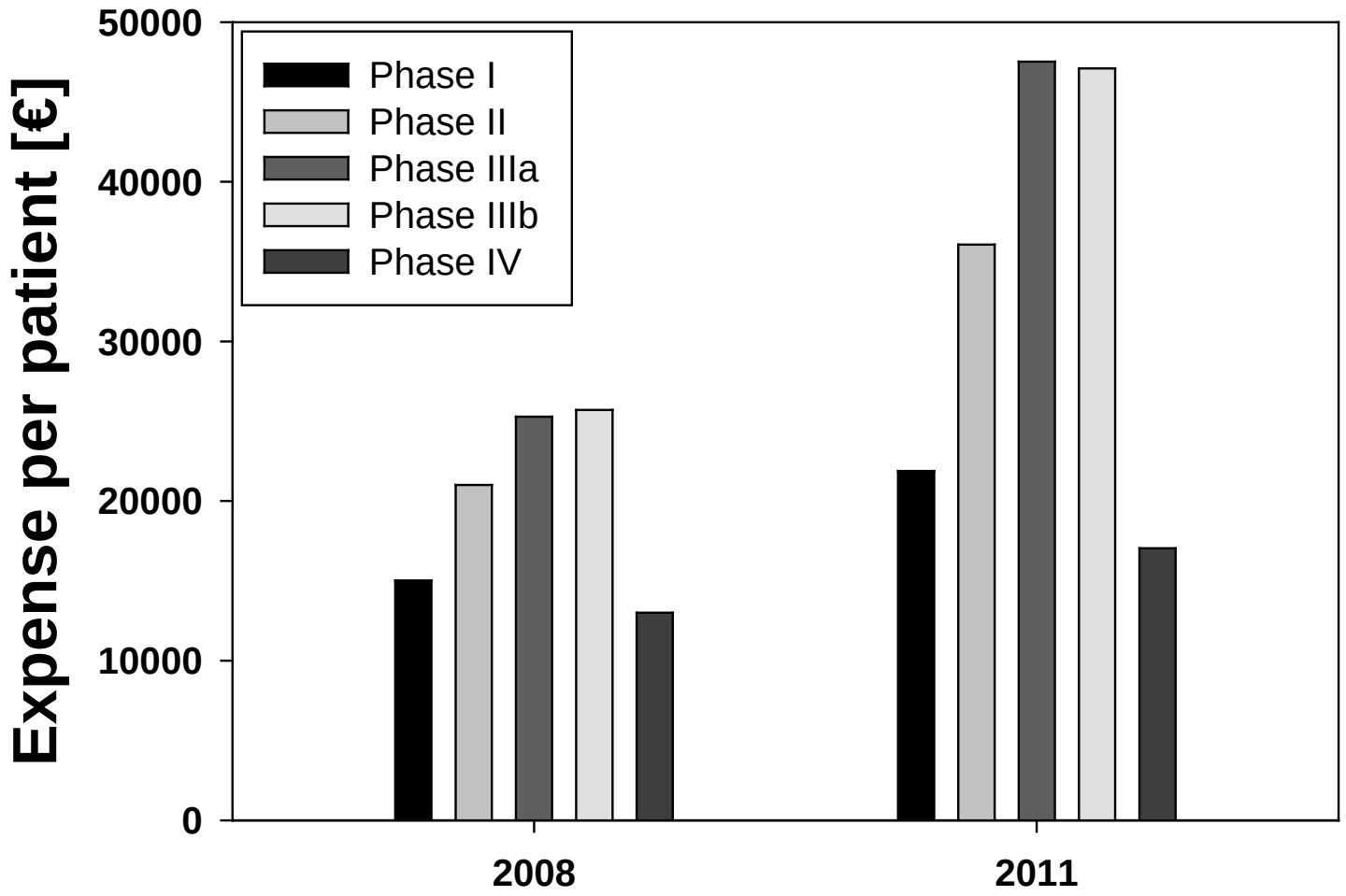
Detail 2: The money question – Costs for clinical trials



Number of patients

Phase1: 20 +

Phase 2: > 50 – 300

Phase3: > 100 - xxx

Data taken from Clinical trial magnifier: http://ctmagnifier.org

Away from translation – but still details?

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Yes!

What are the obstacles for the development of magnesium (alloys) as implant materials?

Material

In vivo veritas?

Standardization

in vitro tests

Application

Alloy design

Transferability

Expectations of medical doctors

Materials – alloy design and development

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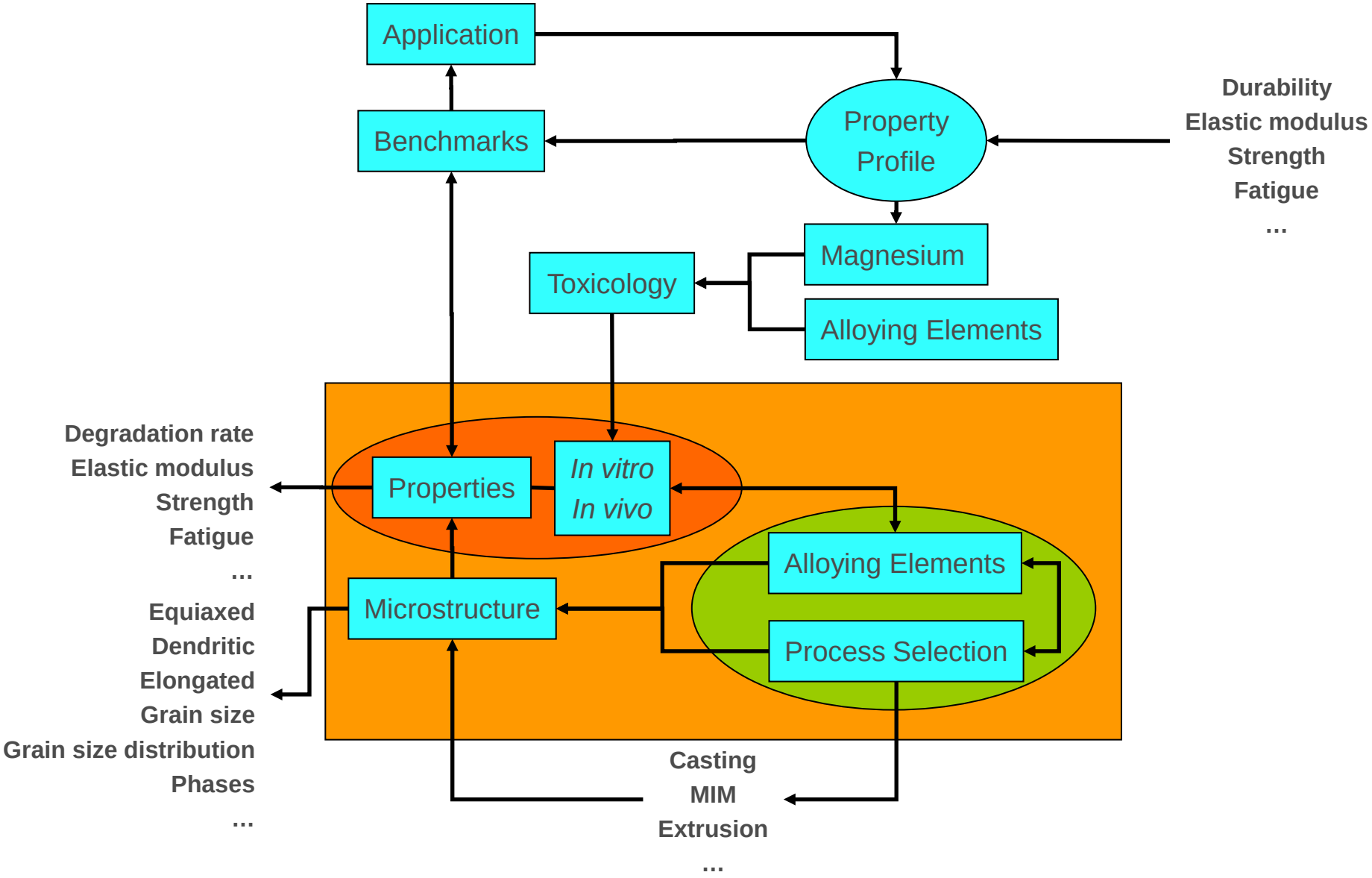

Alloy design -The periodic system of the elements

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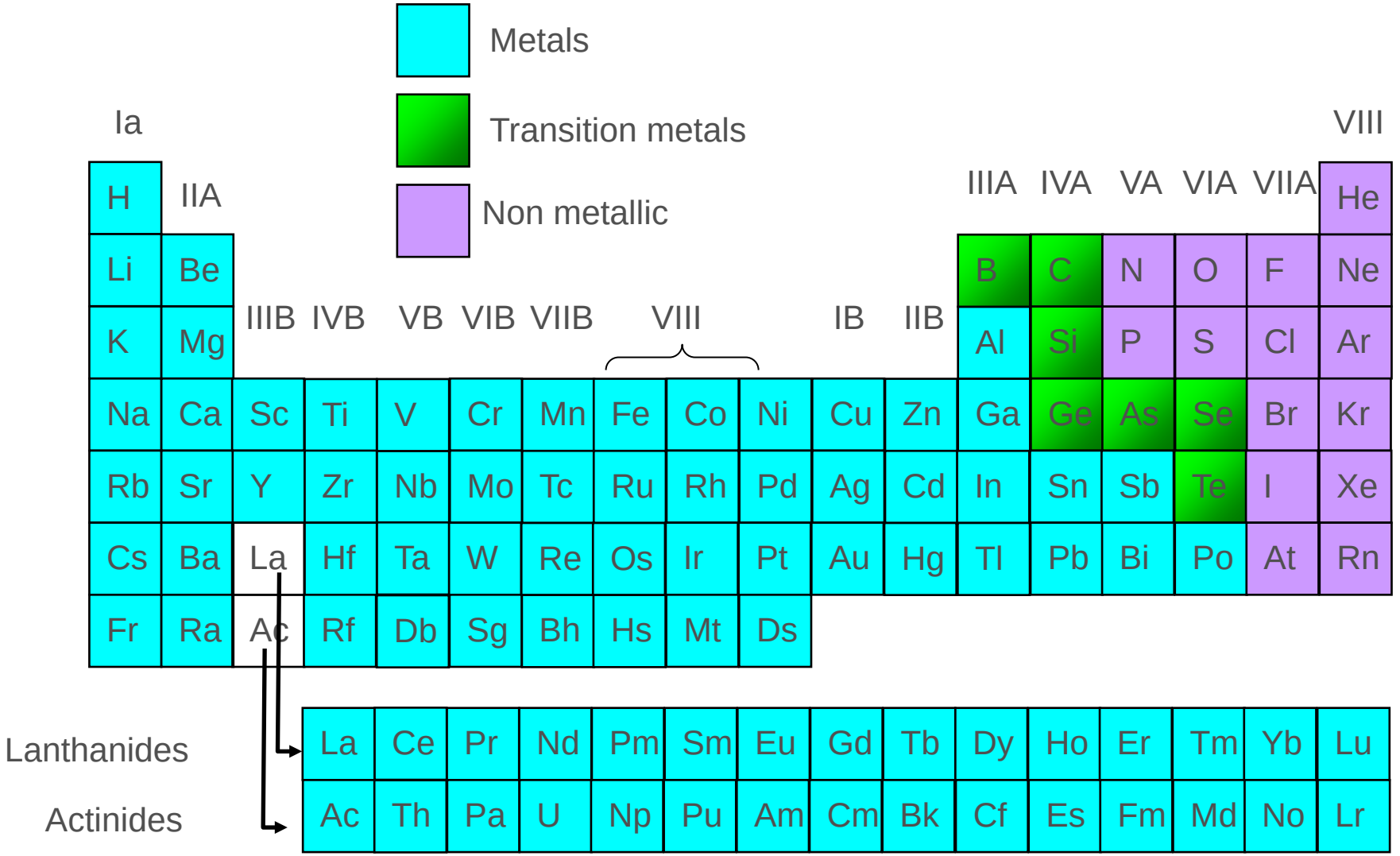
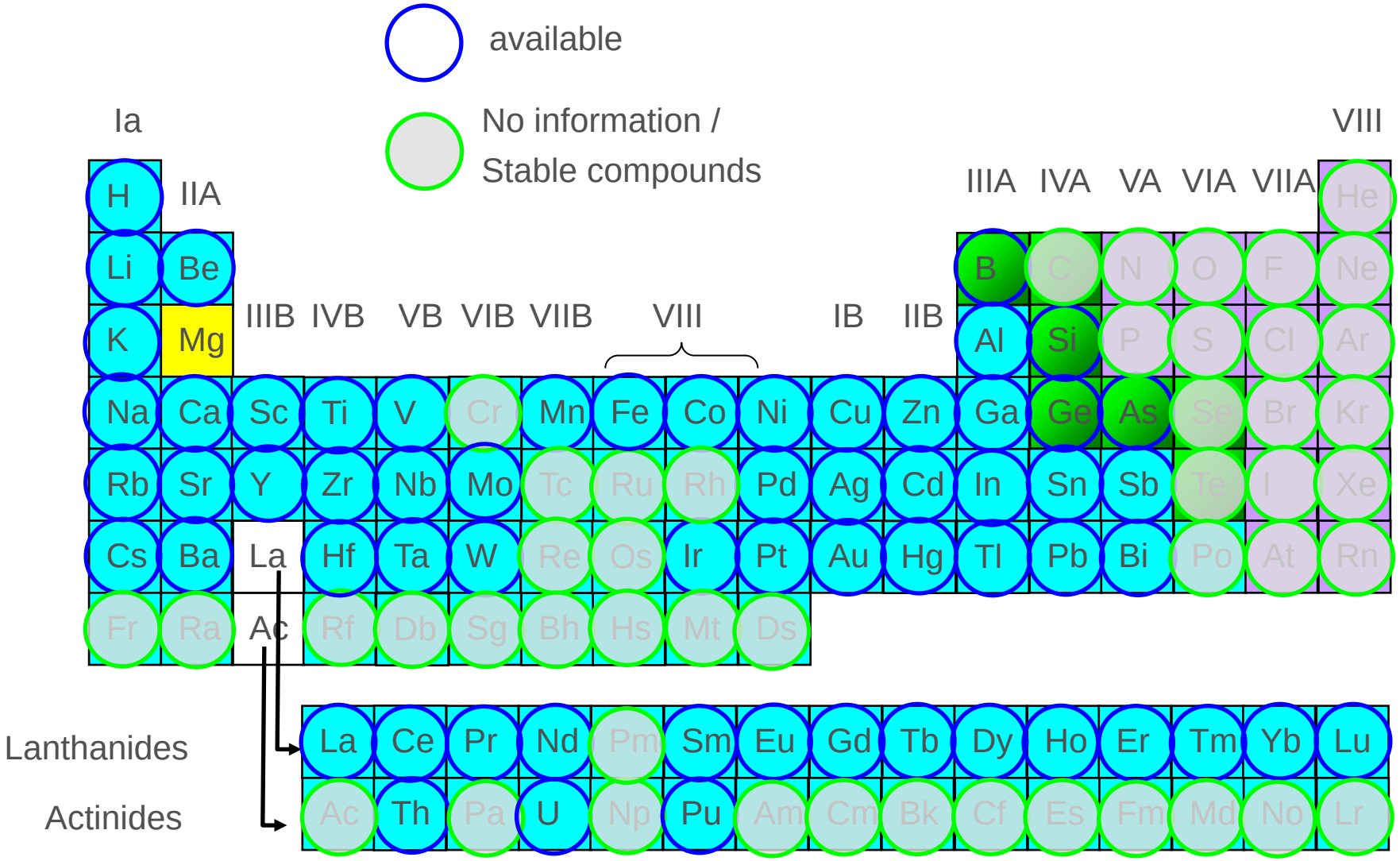
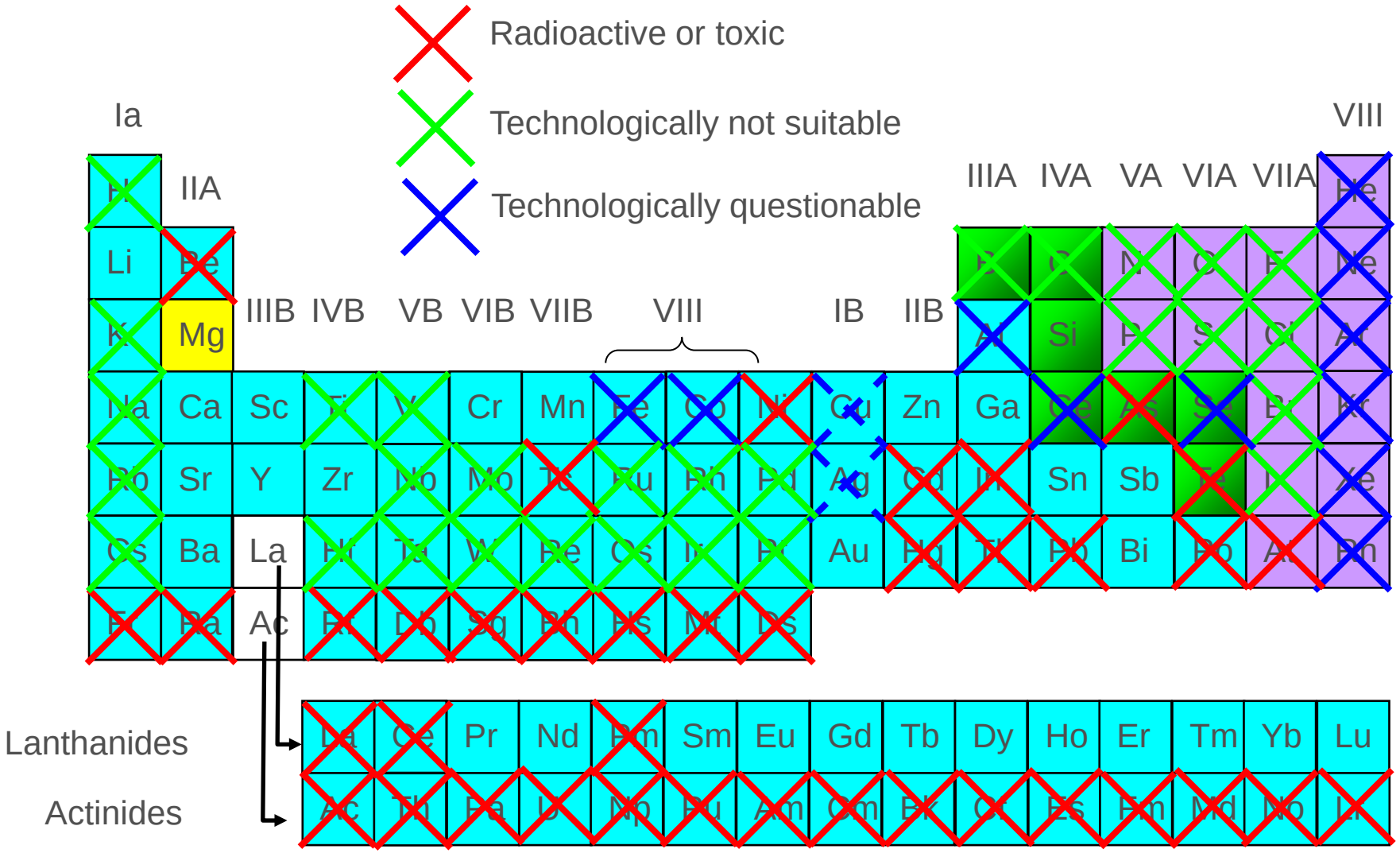


Binary phase diagrams



How to choose alloying elements?



Possible elements with enough information

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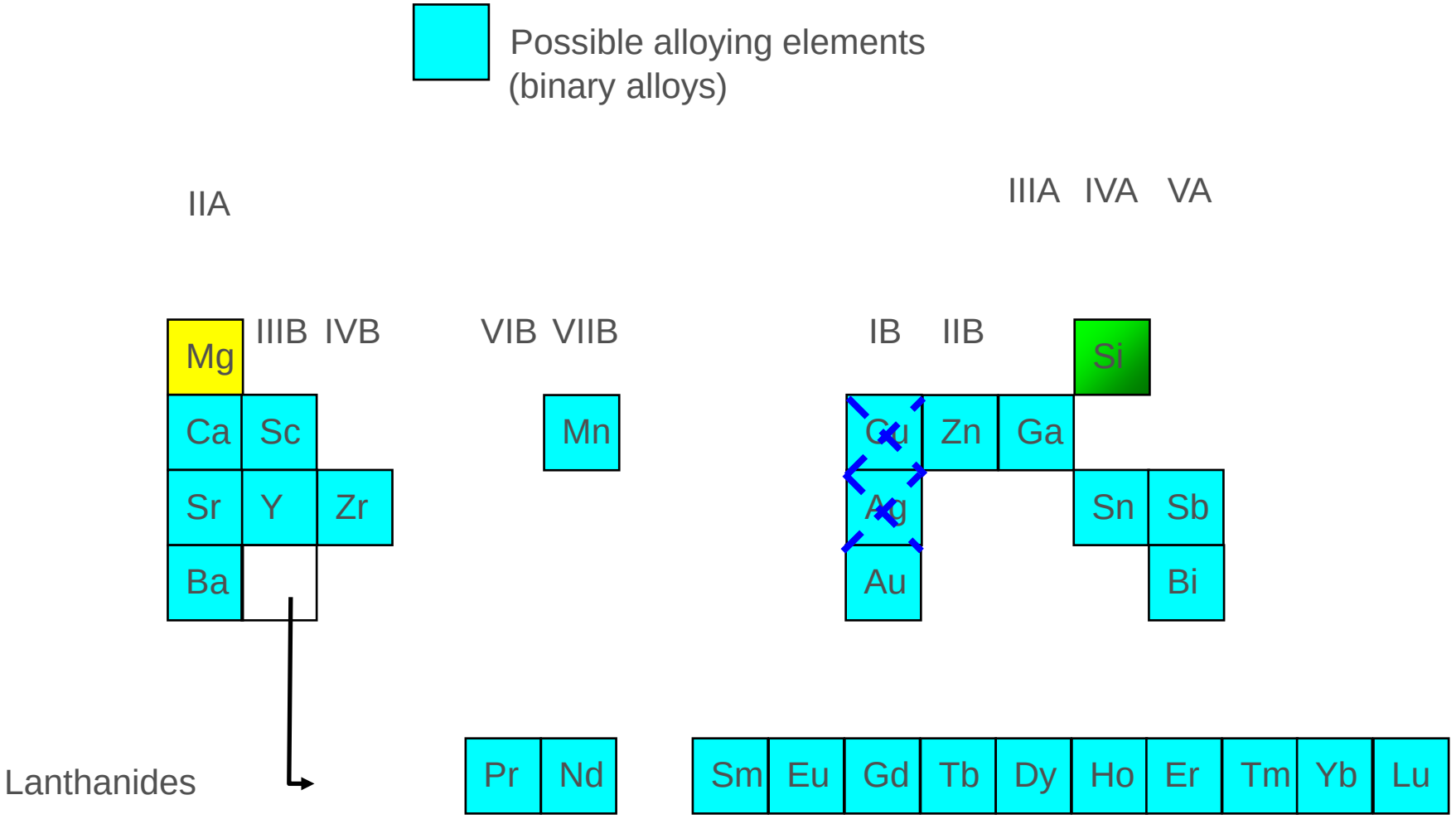

Materials – obstacles

- Microstructure – properties – relation
- Every production step changes the microstructure
- Inhomogeneities in the material lead to localized corrosion
- Every production step can introduce impurities or additional substances
- Cleaning of magnesium surfaces is difficult
- Established methods are optimized for high amounts of material
- For medical products: Good manufacturing practice has to be followed (money!)

Away from translation – but still details?

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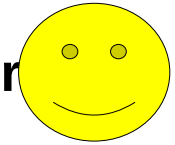
Yes!

What are the obstacles for the development of magnesium (alloys) as implant materials?

Mater



In vivo veritas?

Standardization

in vitro tests

Application

Alloy de

Transferability

Expectations of medical doctors

In vitro tests – the ongoing discussion (ISO 10993)

Which test to use?

Short or long-term tests?

Cell lines or primary cells?

Can tests be simplified?

How „in vivo like“ should the tests be?

Do we need standards?

What information value can be taken from the test?

Comparison of permament and degradable materials

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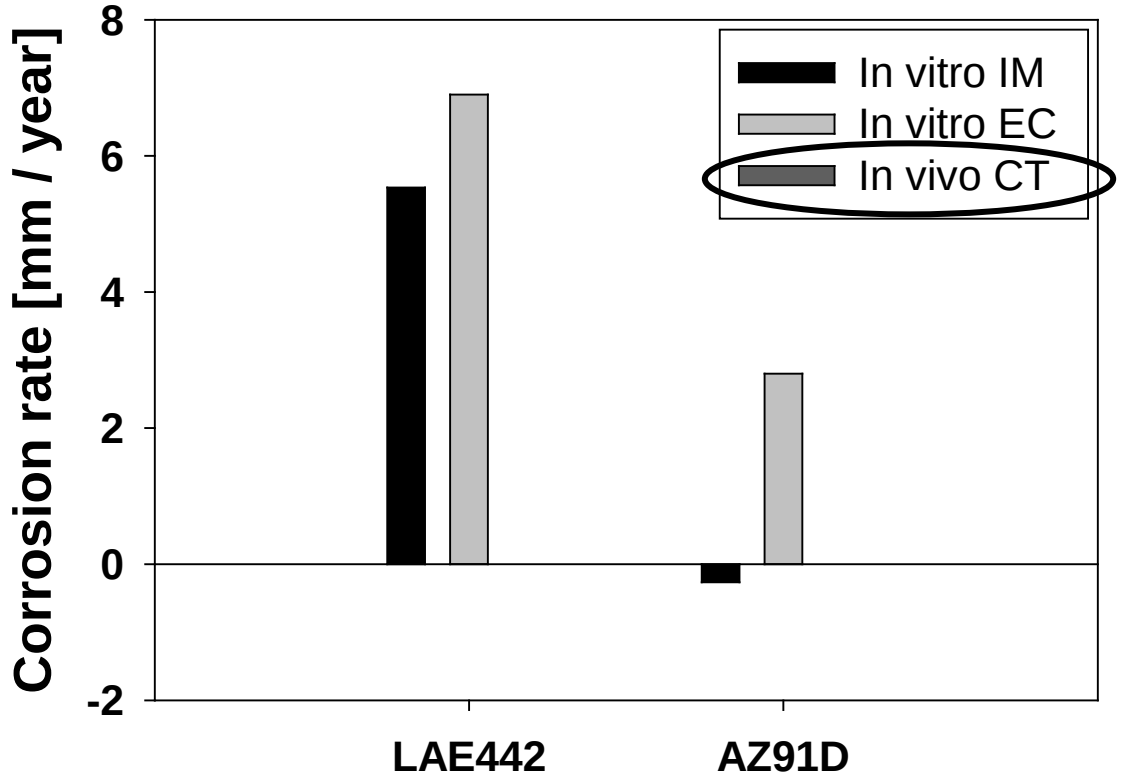
	Permanent
Release of particles / elements	Unwanted / Traces
Mechanical properties	Stable over time
Interaction with tissues	„inert“
Interaction with cells	Material, structure, porosity
Test-environment	Static / dynamic
State of the art (knowledge)	High
Application areas	Ubiquitous

Differences between in vitro and in vivo

Immersion (ASTM-G31-72): Artificial sea water (ASTM-D 1141-98) →In vitro IM

Electrochemistry: Borax-phosphate buffer (DIN 50918) →In vitro EC

In vivo: µ-Computed Tomography →In vivo CT



Witte F, et al. In vitro and in vivo corrosion measurements of magnesium alloys. Biomaterials. 2006;27:1013-8.

Differences between in vitro and in vivo

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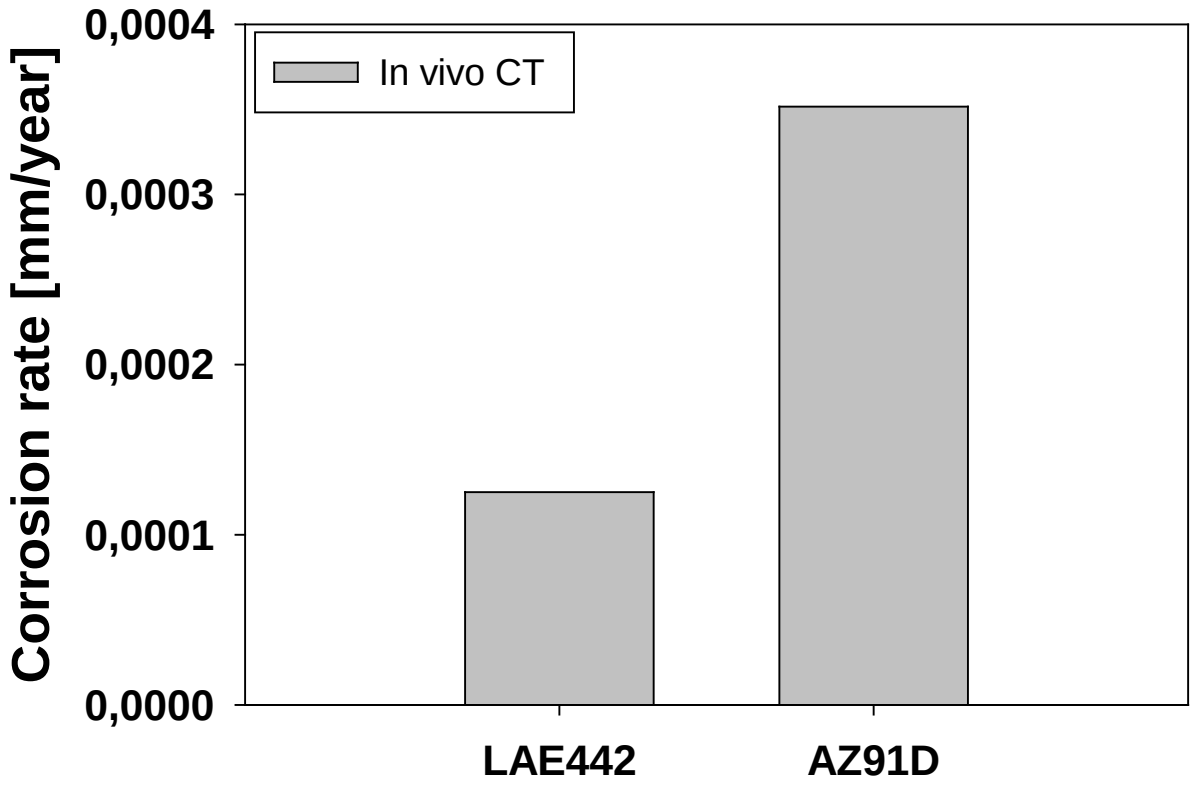


Witte F, et al. In vitro and in vivo corrosion measurements of magnesium alloys. Biomaterials. 2006;27:1013-8.

How to overcome this?

Problem: only *in vivo* experiments are reliable!

Alloy →  → **Result**

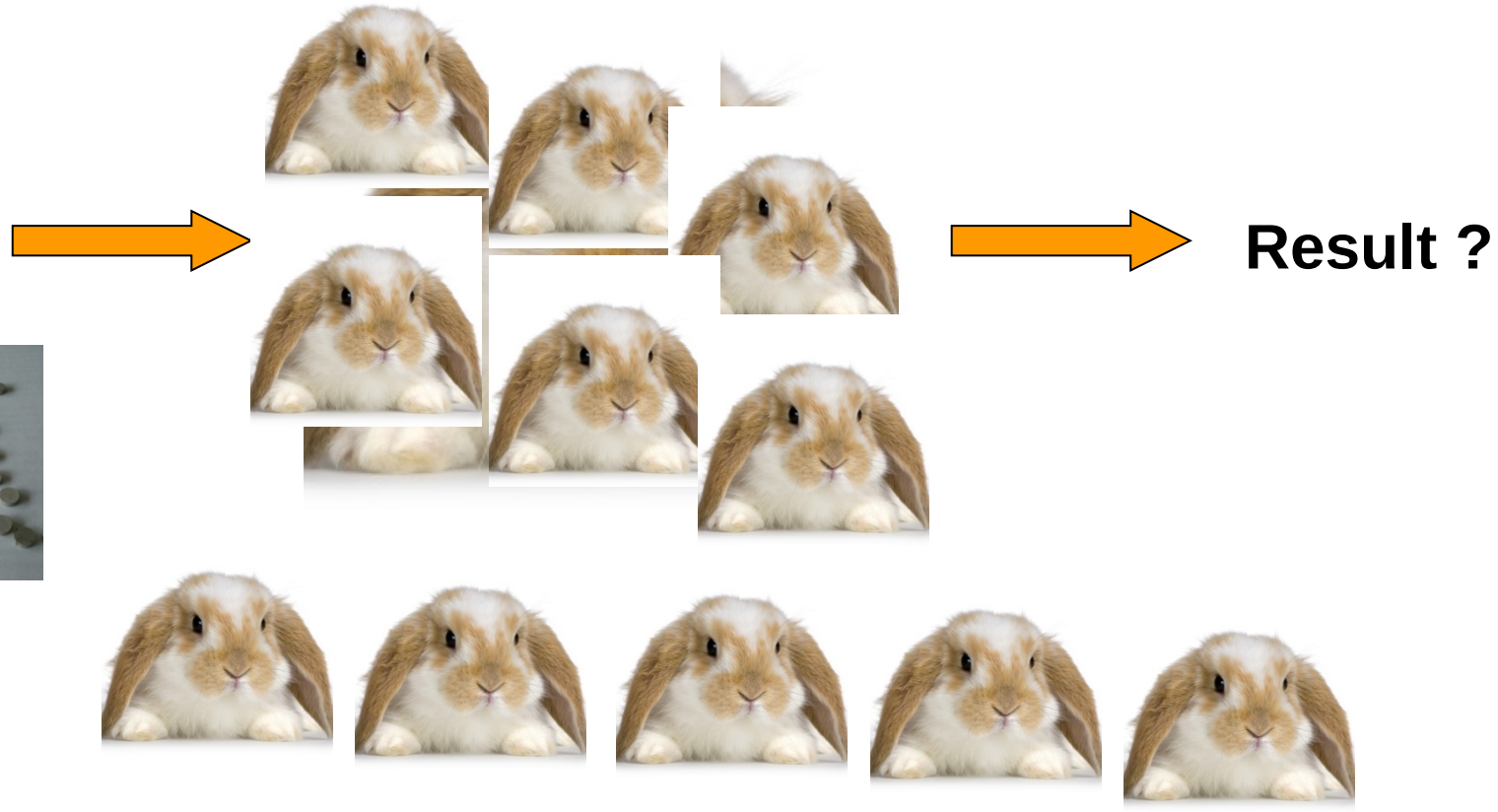
Witte et al. Biomaterials 27 (2006) 1013-1018

How to overcome this?

Problem: only *in vivo* experiments are reliable!

Alloying

System



Result ?

We have to develop in vitro Setups!

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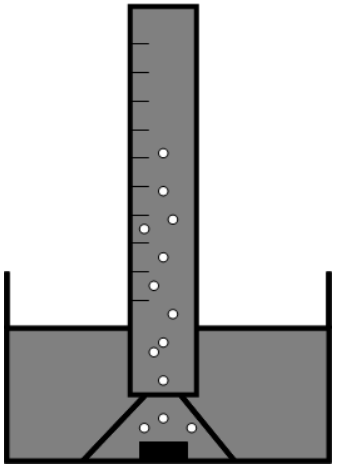
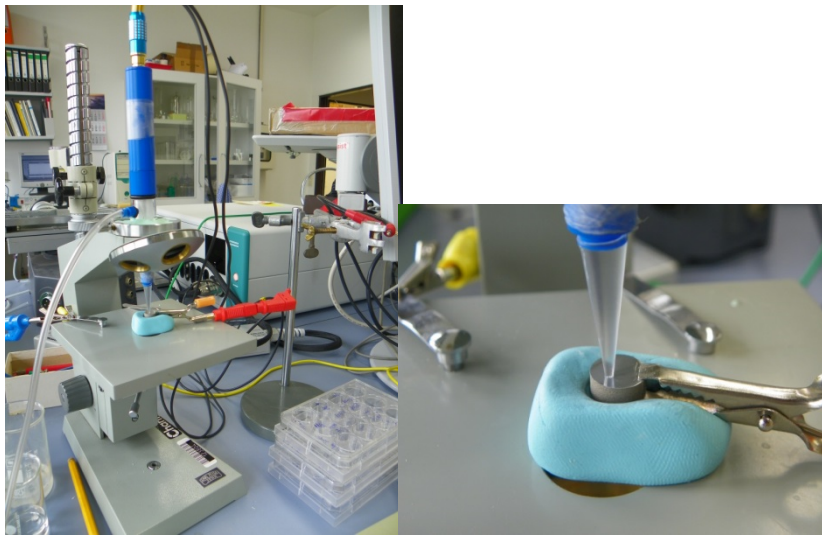
Eudiometer



Electrochemical setups



W.D. Müller, Charité Berlin, Germany

Cell culture

Parameters (technical):

Short term measurements (EC)
Long term measurements (Eudiometer)
37° C
Atmospheric pressure
Physiological solutions

Solutions:

Water
Artificial sea water
Physiological saline
Hank‘s balanced salt solution (HBSS)
Dulbecco‘s modified eagle medium (DMEM)
Simulated body fluid (SBF)

We have to develop in vitro Setups!

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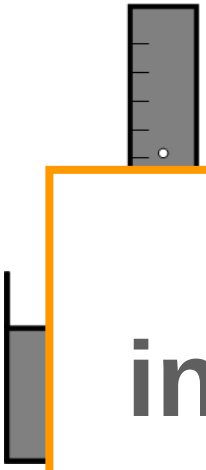
Eudiometer



Electrochemical setups

Cell culture

How does the environment influence magnesium corrosion *in vitro*?

Parameters (technical):

Short term measurements (EC)
Long term measurements (Eudiometer)
37° C
Atmospheric pressure
Physiological solutions

Solutions:

Water
Artificial sea water
Physiological saline
Hank‘s balanced salt solution (HBSS)
Dulbecco‘s modified eagle medium (DMEM)
Simulated body fluid (SBF)

One caveat for in vitro tests

Magnesium chloride ≠ Magnesium extract

The factors for this effect have to be elucidated

Possible candidates:

- Relation between Mg and Ca
- Proteins
- Maybe you have a good idea?

In vitro - Extraction procedures (ISO 10993)

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Table 1 — Standard surface areas and extract liquid volumes

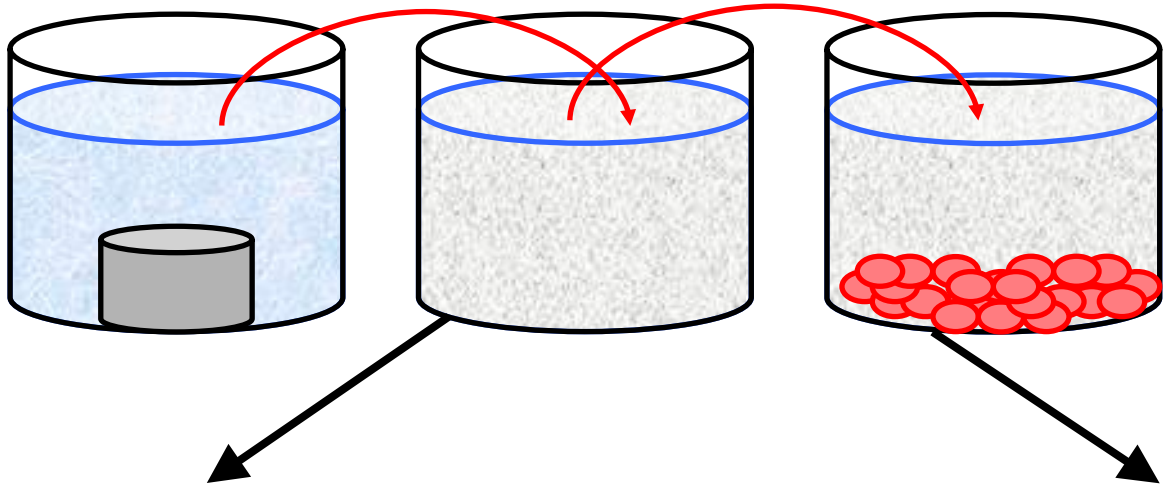
Thickness mm	Extraction ratio (surface area or mass/volume) ± 10 %	Examples of forms of materials
< 0,5	6 cm^2/ml	film, sheet, tubing wall
0,5 to 1,0	3 cm^2/ml	tubing wall, slab, small moulded items
> 1,0	3 cm^2/ml	larger moulded items
> 1,0	1,25 cm^2/ml	elastomeric closures
Irregularly shaped solid devices	0,2 g sample/ml	powder, pellets, foam, non-absorbent moulded items
Irregularly shaped porous devices (low density materials)	0,1 g/ml	membranes
NOTE While there are no standardized methods available at present for testing absorbents and hydrocolloids, the following is a suggested protocol. Determine the volume of extractiom vehicle that each 0,1 g or 1,0 cm^2 of material absorbs. Then, in performing the material extraction, add this additional volume to each 0,1 g or 1,0 cm^2 in an extraction mixture.		

Mg-alloy: 16 x 16 x 5 mm; weight ~ 3 g; Surface area 8.32 cm^2

Extraction volume: By weight (0.2 g/mL): 15 mL

By surface area (3 cm^2/mL): 2.77 mL - By surface area (1.25 cm^2/mL): 6.66 mL

Extract preparation according to ISO 10993



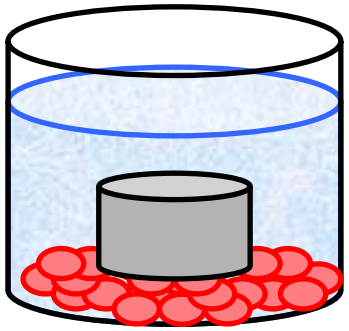
0.2 g Material per mL Medium + serum
72 hours, 37°C
Test with cell lines

Characterisation of Extracts

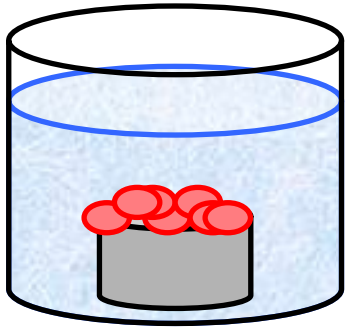
Characterisation of Cell reaction

Other possibilities

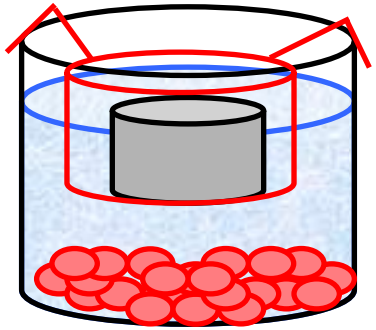
Direct test (Material on cells)



Direct test (Cells on Materials)

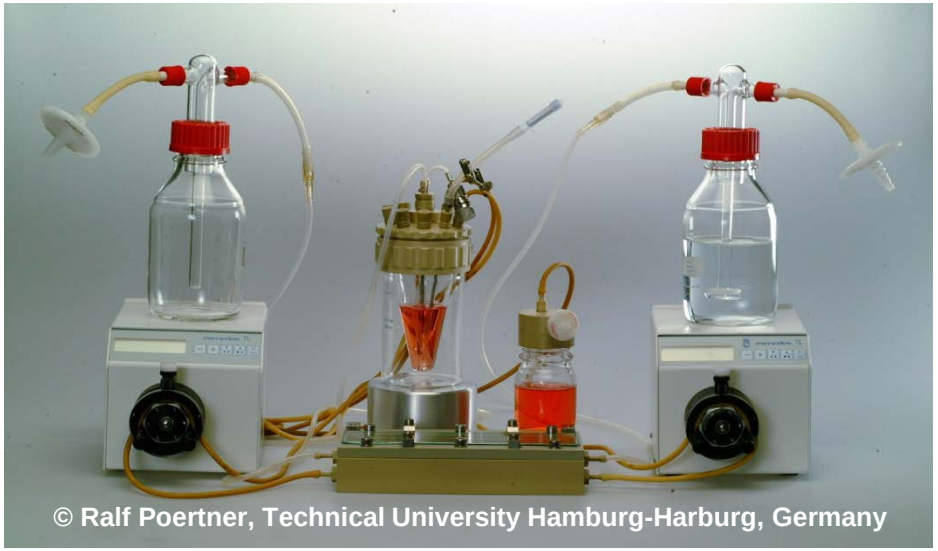


Non-contact test



Closer to reality:

Dynamic testing in a bioreactor



Relevance of Cell culture conditions (CCC)

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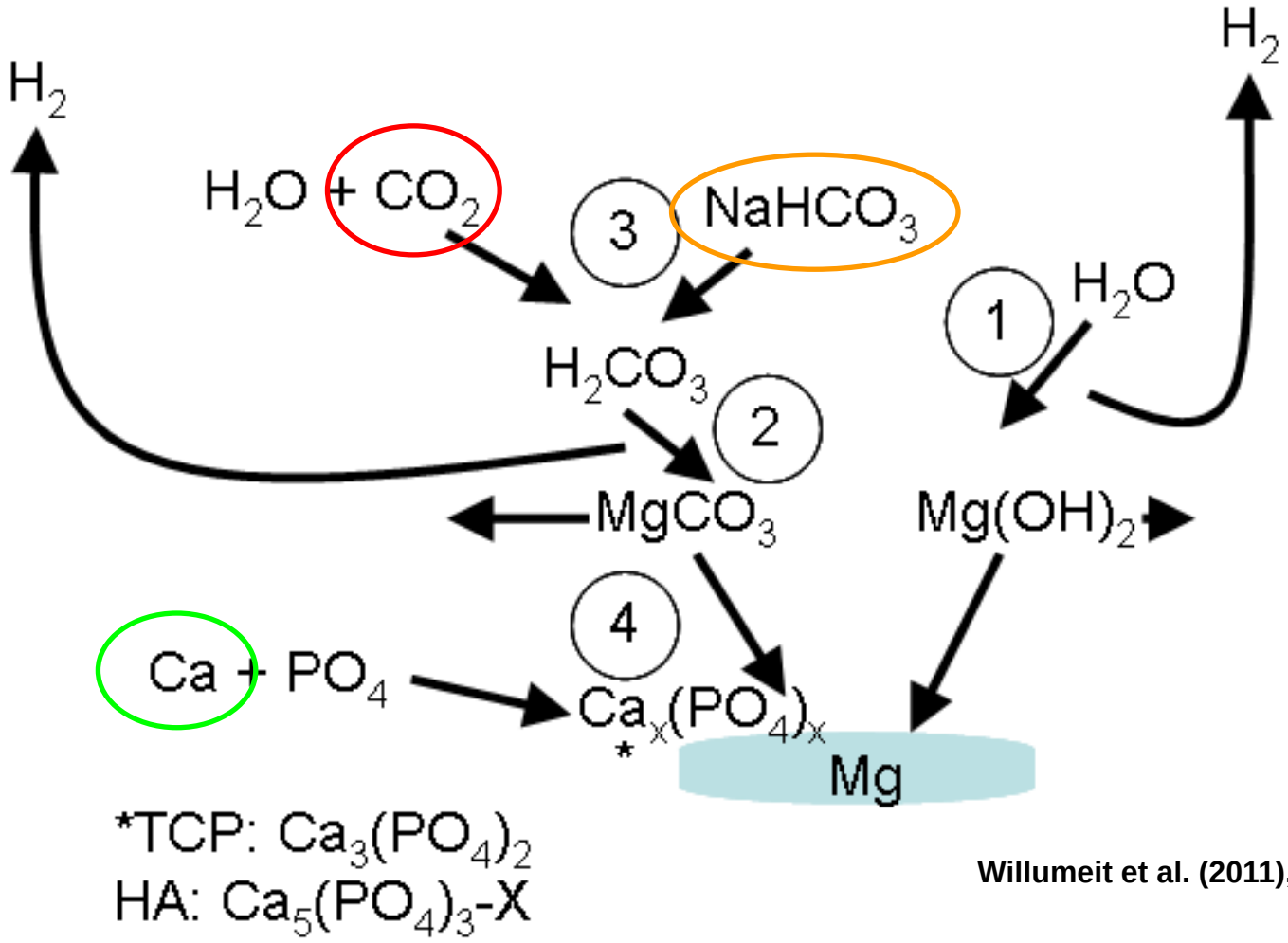
Atmospheric conditions: 20°C, 20% O_2, 0.034% CO_2, 40-60% relative humidity

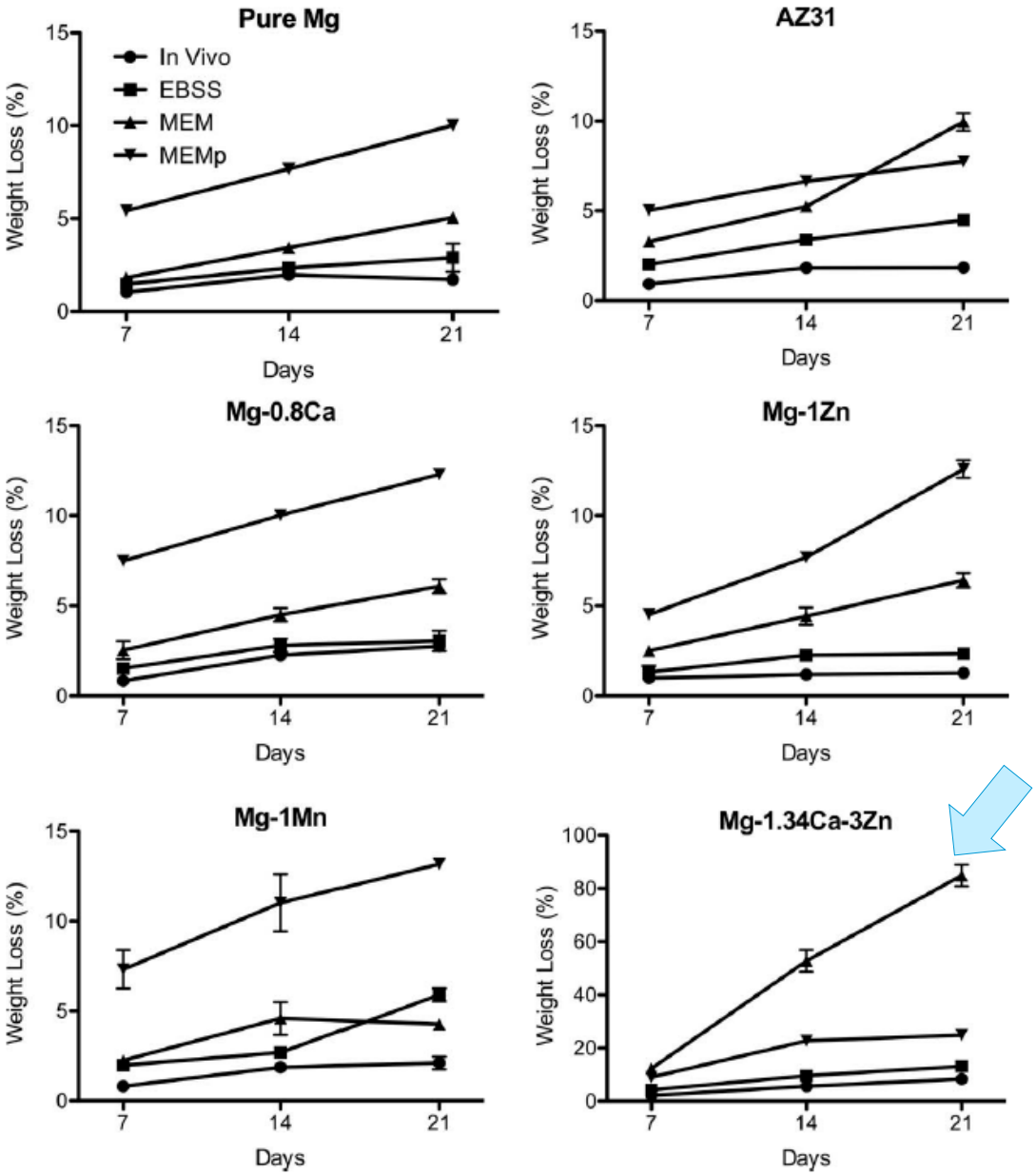
Cell Culture Conditions: 37°C, 20% O_2, 5% CO_2, 95% relative humidity



1: „Standard reaction“
2: **Introduction of CO_2**
3: **Buffering system**
4: **Biomineralization**

Willumeit et al. (2011), Acta Biomaterialia 7, 2704-2715

In vitro prediction ?



EBSS: Earle‘s balanced salt solution

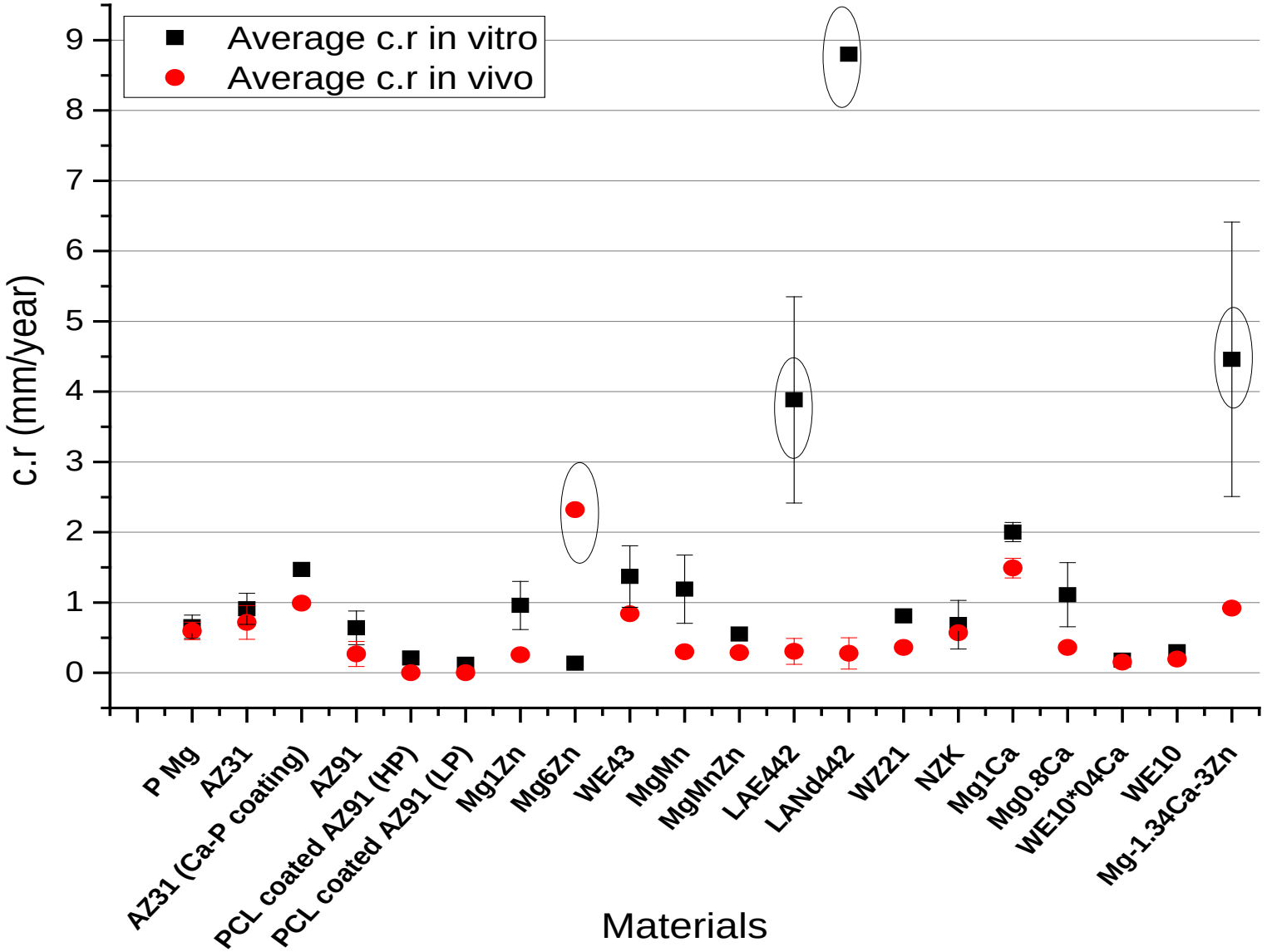
MEM: Modified Eagle Medium

MEMp: MEM + Proteins

In vivo: subcutaneous implantation in rats

Walker J, Shadanbaz S, Kirkland NT, Stace E, Woodfield T, Staiger MP, et al. Magnesium alloys: Predicting in vivo corrosion with in vitro immersion testing. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2012;100B(4):1134-41.

Correlations?

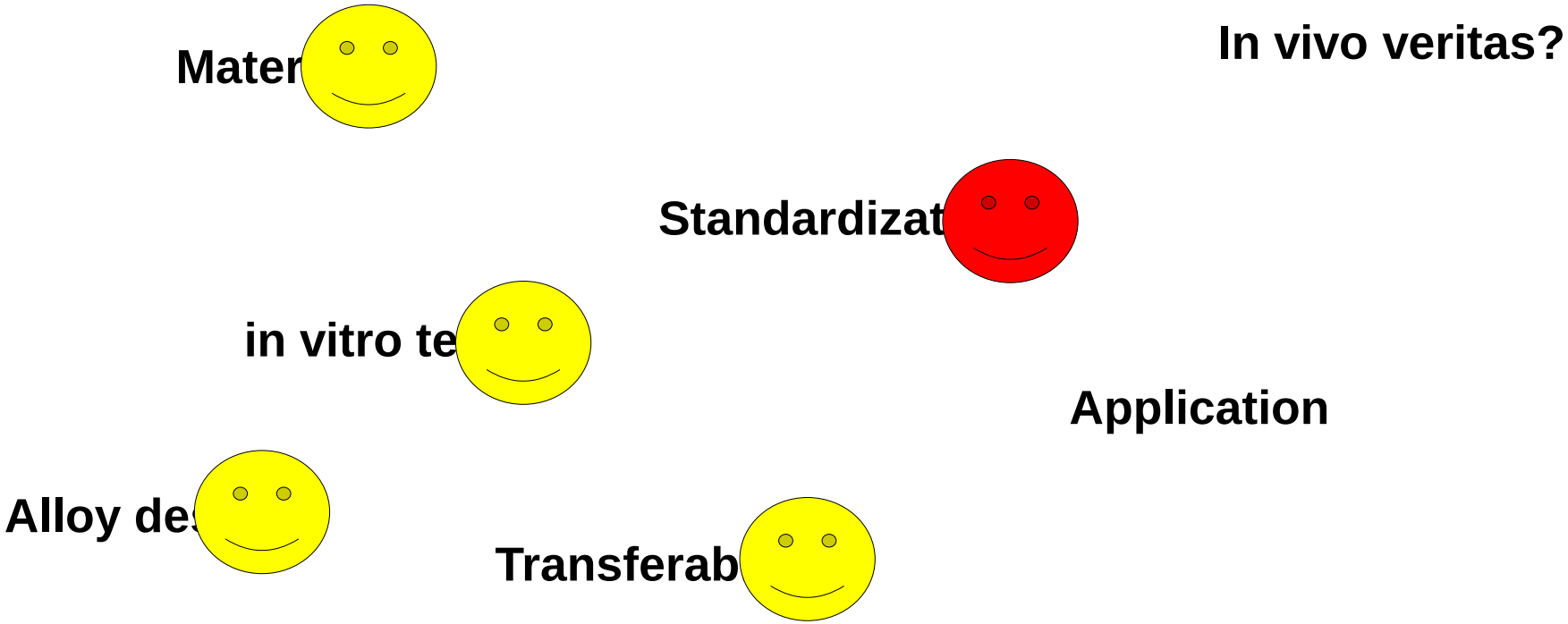


Literature Review by Helvia Martinez, in preparation

Away from translation – but still details?

Yes!

What are the obstacles for the development of magnesium (alloys) as implant materials?



In vivo tests – also an ongoing discussion

Which animal to use?

Short or long-term tests?

Which implantation site?

Are the results transferable to humans?

Which parameters to analyse?

Can we monitor in vivo „online“?

Which informations have to be taken from the test?

Hydrogen absorption capacity

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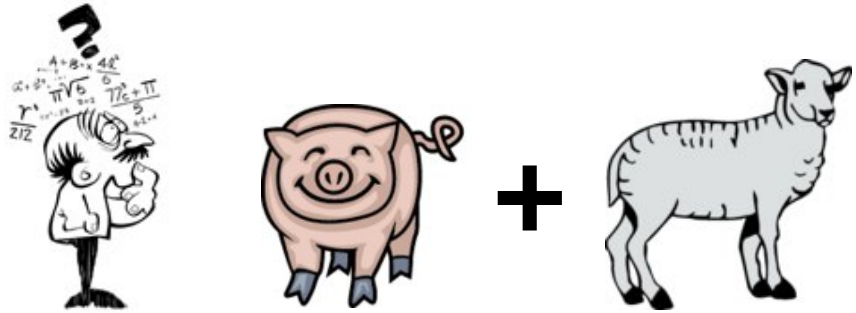
Witte et al., COSSMS, Vol.12 (5-6),2008: 63-72

	Water content [%]	Blood flow [ml/min/100g]	Water content [%]	Blood flow [ml/min/100g]	Water content [%]	Blood flow [ml/min/100g]
Heart	79.0 ± 0.2	39	78.2-79.0	50.0 ± 0.8	71.2-80.3	1000
Skin	65.1 ± 0.7	18.9 ± 1.4	54.0-67.8	12.7 ± 1.7	67.8-75.8	120
Bone	44.6 ± 1.7	2.3 ± 2.0	39.2-58.1	19.1 ± 1.7	43.9	120



Slide courtesy by Frank Witte

Corrosion rate is dependent on anatomical site!

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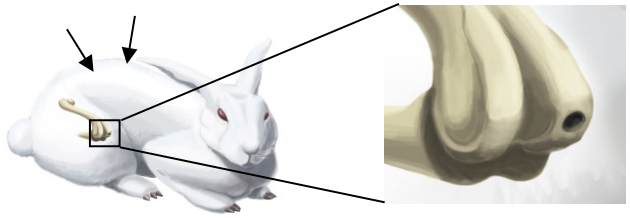
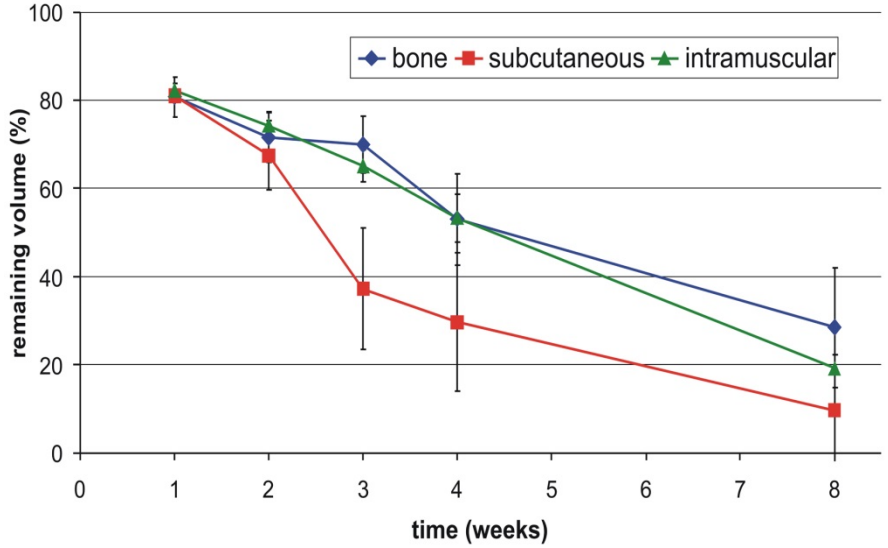
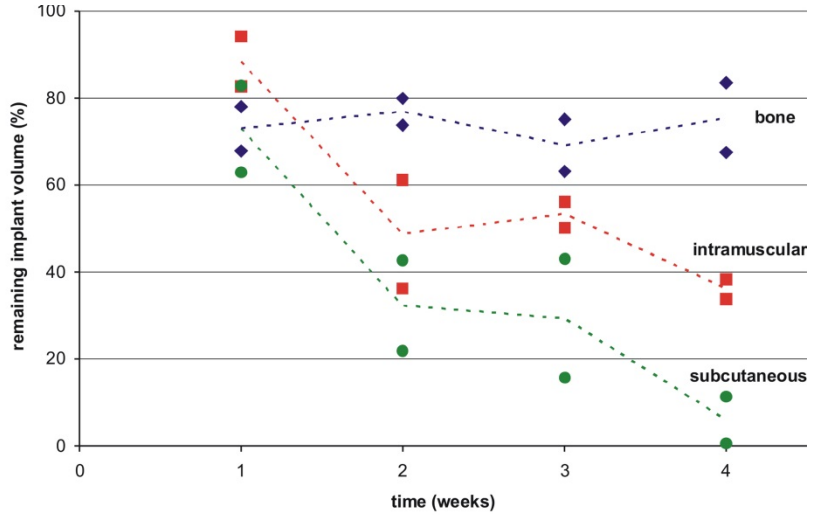
New Zealand White Rabbit





RS66, cylinder 3x5 mm



HP-MgBiCa, cylinder 3x5 mm

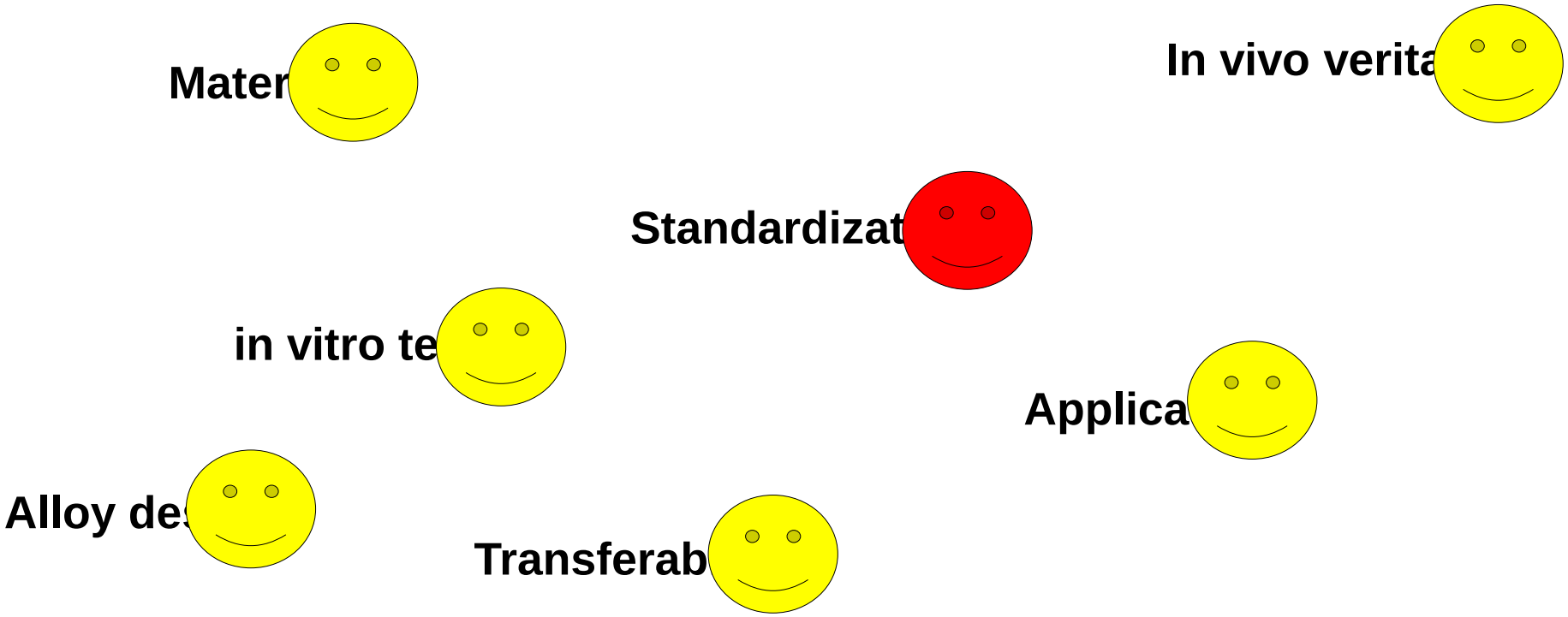
Corrosion rate: subcutaneous > intramuscular > bone

Slide courtesy by Frank Witte

Away from translation – but still details?

Yes!

What are the obstacles for the development of magnesium (alloys) as implant materials?



Expectations of medical doctors

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Magnesium burns, or not?

Does the material have the same properties as permanent implants?

Why should a material degrade?

Is it more expensive?

What happens if I put this in a diabetic patient?

I have bad experience with degradable polymers, why should this be better?

When can I put this in the patient?

I do not like this material!

A short break!

How can translation work?

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Company strategies

Case 1: Biotronik

Mid 1990s: Idea to use magnesium alloys as base material for degradable stents
Material choice: commercial WE43 (alloy for high temperature applications), Patent from Magnesium Elektron Ltd., Manchester, UK

1998: First animal experiment (New Zealand white rabbits), published in 2001

2000: Second animal experiment (Minipig), published in 2003

2002: Safety and efficacy study (Minipig), published in 2006

2003: BEST BTK – “First in Man Below the Knee” peripheral clinical use

30.05.2004: First implantation of coronary stents in humans (PROGRESS-AMS study), published in 2007
-> results comparable to Bare metal stent

2003/2004: Drug eluting stents enter the market (Cordis / Boston Scientific)

2008: First results on DREAMS (Drug-eluting absorbable metal stent) + clinical studies

ATMP?

→ No product on the market, but a lot of money went into research

How can translation work?

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Company strategies

© Syntellix Ag

Case 2: Syntellix

Everything was done according to the hellish details

- Venture capital available
- From the idea to the market (CE) in 5 years
- Network to clinicians, producers and research was available
- Extended quality managment
- Dedicated marketing

→ Entrance to a new market, market leadership for the next years granted!

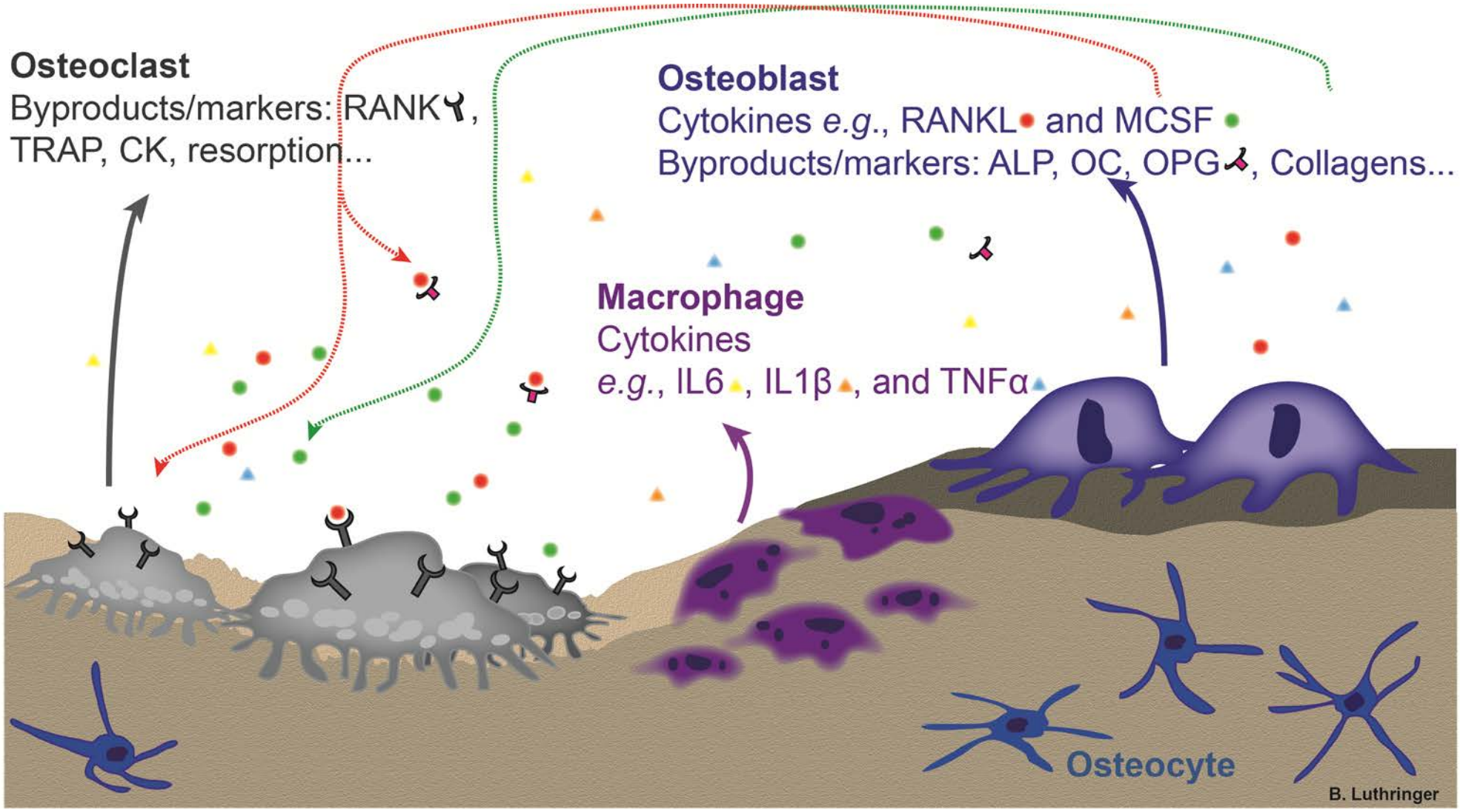
Summary

Translation can work!

BUT!!!!!!!!!

A lot more of systematic (!) research is necessary to understand the underlying mechanisms

Cytotoxicity issues – the tissue question



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Thank you!

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