Dissolucytotic liberation of gold ions from gold implants

Gold ions cause immunosuppresion making metallic gold interesting from a clinical point of view

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Gold ions inhibit lysosomal enzymes and reduces the number of macrophages and the production of cytokines

The immuno-modulatory effects of gold ions have been used for the treatment of diseases with autoimmune pathology such as rheumatic and psoriatic arthritis for more than 50 years (Klippel and Dieppe 1994). Gold ions have been found to alter the behaviour of macrophages and other phagocytotic cells by **inhibiting lysosomal enzymes** and **reducing both the number of macrophages and the production of cytokines** in synovial tissue of patients rheumatic arthritis (Persillin and Ziff 1966; Yanni et al. 1994).

Gold ions suppress NF-κ B binding activity and inhibit I- κ B-kinase activation

The reduced production of pro-inflammatory cytokines has been related to the ability of gold ions to **suppress NF-κ B binding activity and I-κ B-kinase activation**.

In this context it is worth mentioning that gold ions have been found to **inhibit antigen processing** (Yang et al. 1995 ; Traber et al. 1999; Yoshida et al. 1999).

Gold ions suppress inflammation

Systemic treatment with gold ion containing drugs, the socalled ”gold cure” has been an acknowledged approach for treatment of articular rheumatism at hospitals all over the world for more than thirty years, with the medical precaution that excess treatment causes kindney damage

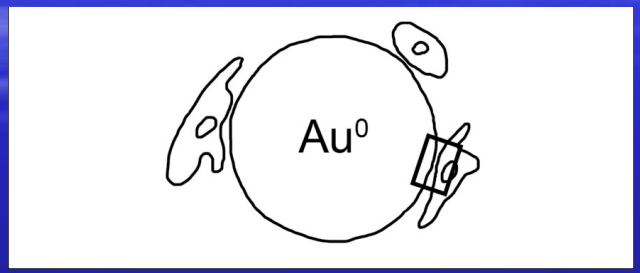
Metallic gold might circumvent the toxicity problems of gold ions

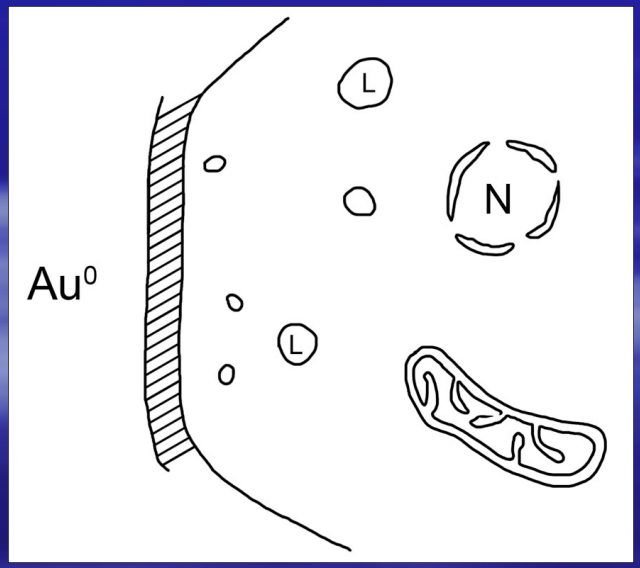
The amount of gold ions liberated by dissolucytosis of metallic gold surfaces (*in vivo* gold particles/implants) is rather limited in number, compared to the amount released by intramuscular treatment with a gold-thio- compound e.g. Aurothiomalate (Myocrisin ®) – “The gold cure”

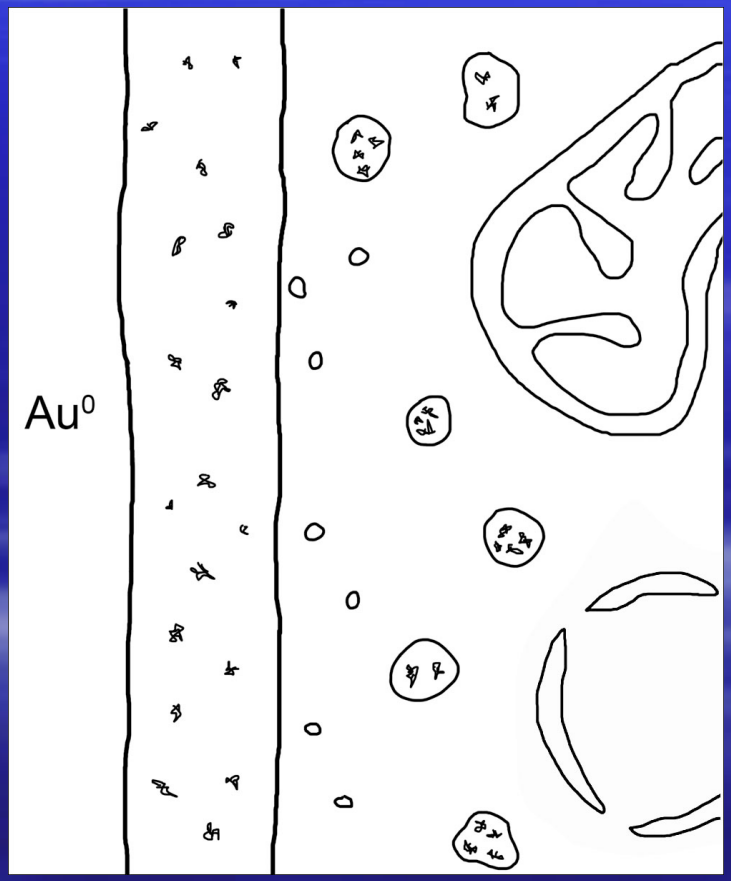
Local Gold Cure

As the gold ions liberated from gold implants/gold particles are taken up in particular by immunoreactive cells like macrophages and mast cells adjacent to the metalic gold surfaces, metallic gold causes a safe local gold Cure

Gold ions are liberated from gold implants/particles bigger that 20 microns by a process coined dissolucytosis







The dissolucytotic release of gold ions is caused by the chemical milieu in the dissolution membrane

$$4Au + 8CN + O_2 + 2H_2O = 4Au(CN)_2^- + H_2$$

Aurocyanide is found in the urine of patients

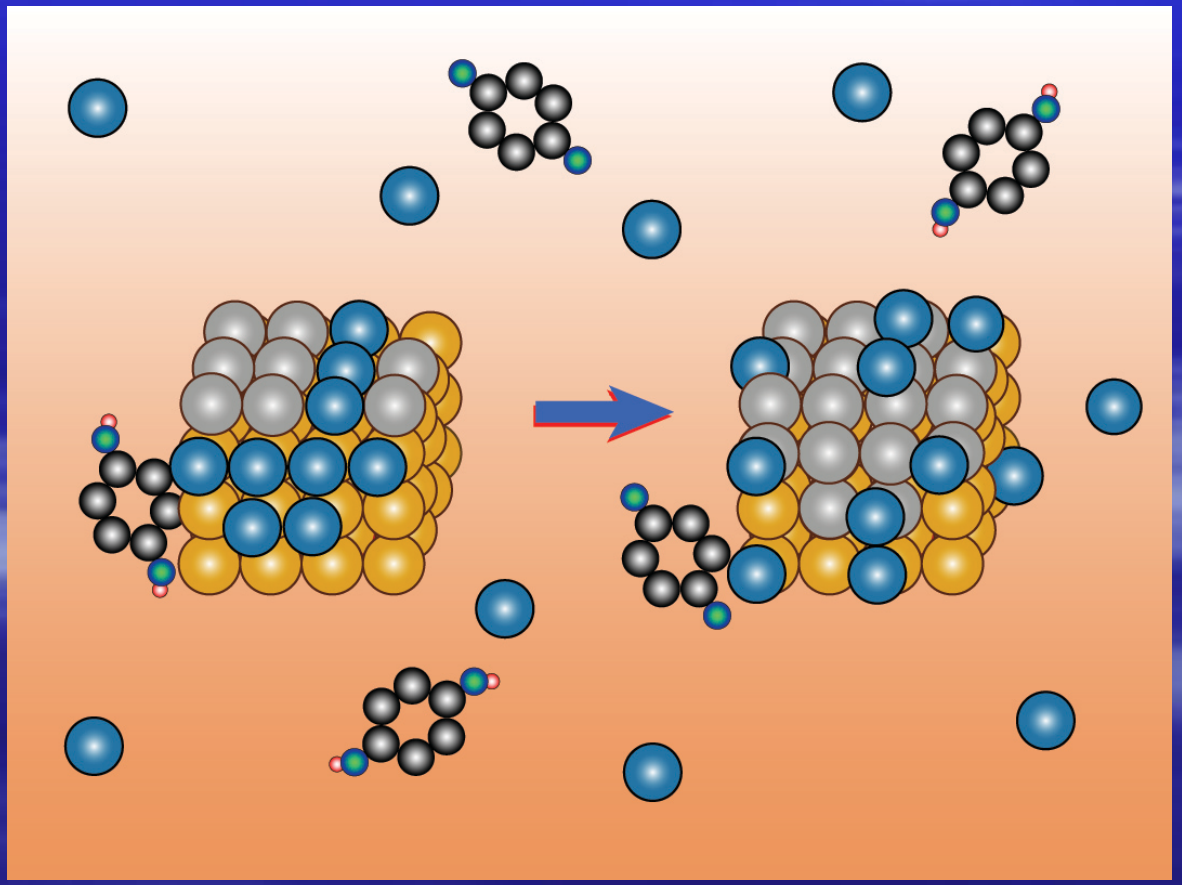
Treated with (Myocrisine ®)

AUTOMETALLOGRAPHY

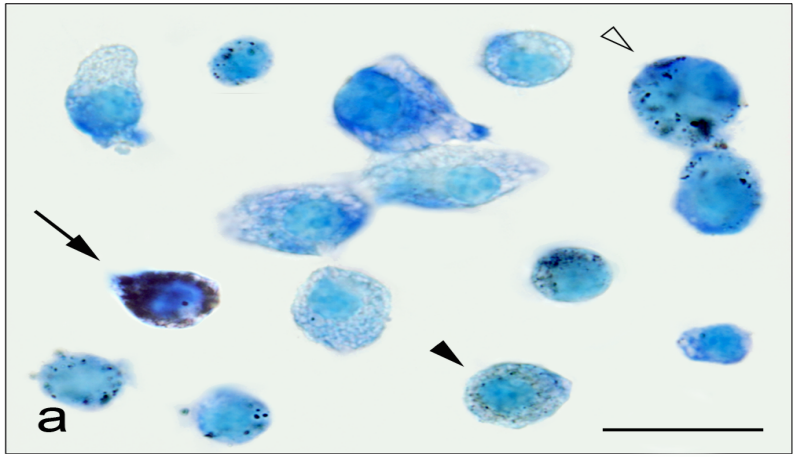
If gold ions are reduced, e.g. being radiated with UV light, the resulting gold atoms will create quantum dots that can be Silver enhanced by AMG

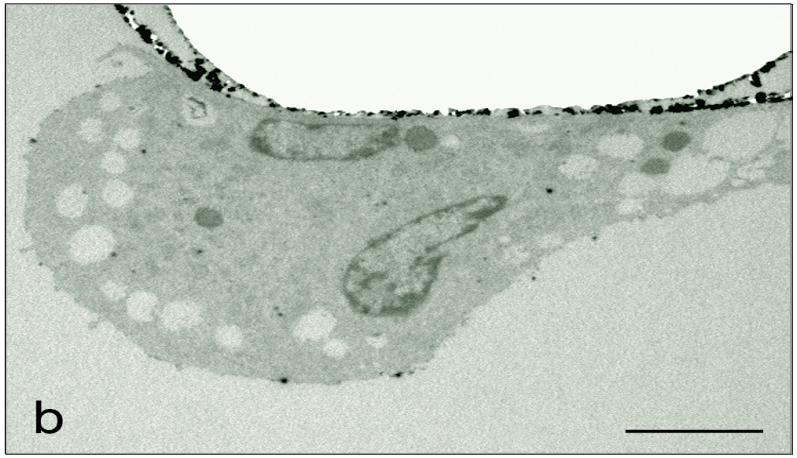
- Gold catalyse the reduction of silver ions to metallic silver atoms if electrons are available
- The electron donor is hydroquinone
- The AMG process give rise to growing silver shells around each quantum dot

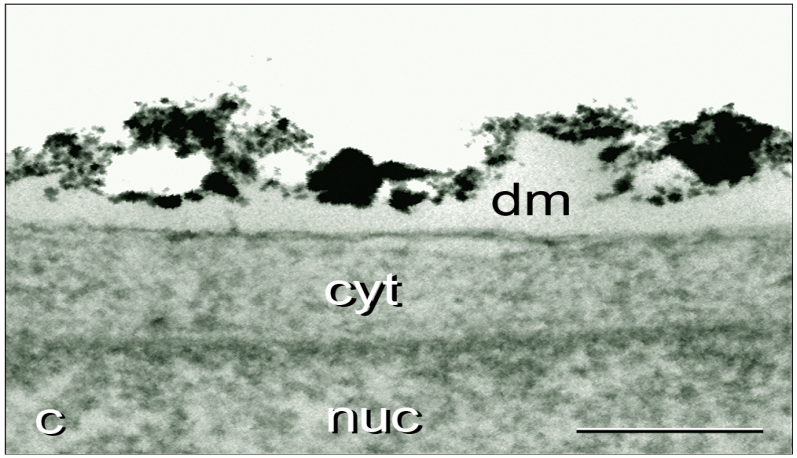
AMG
autometallography



In vitro dissolucytosis
of metallic gold particles

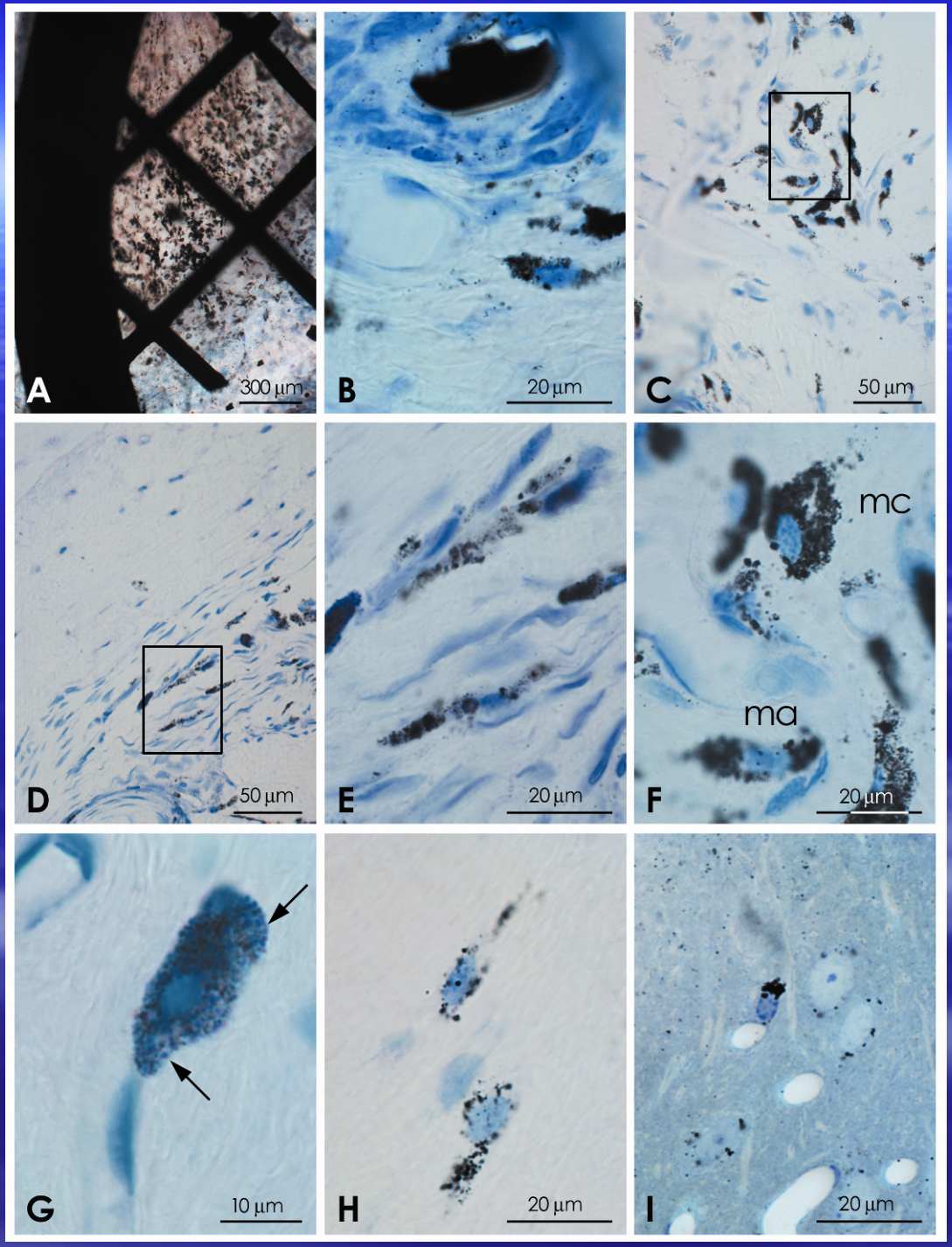

a

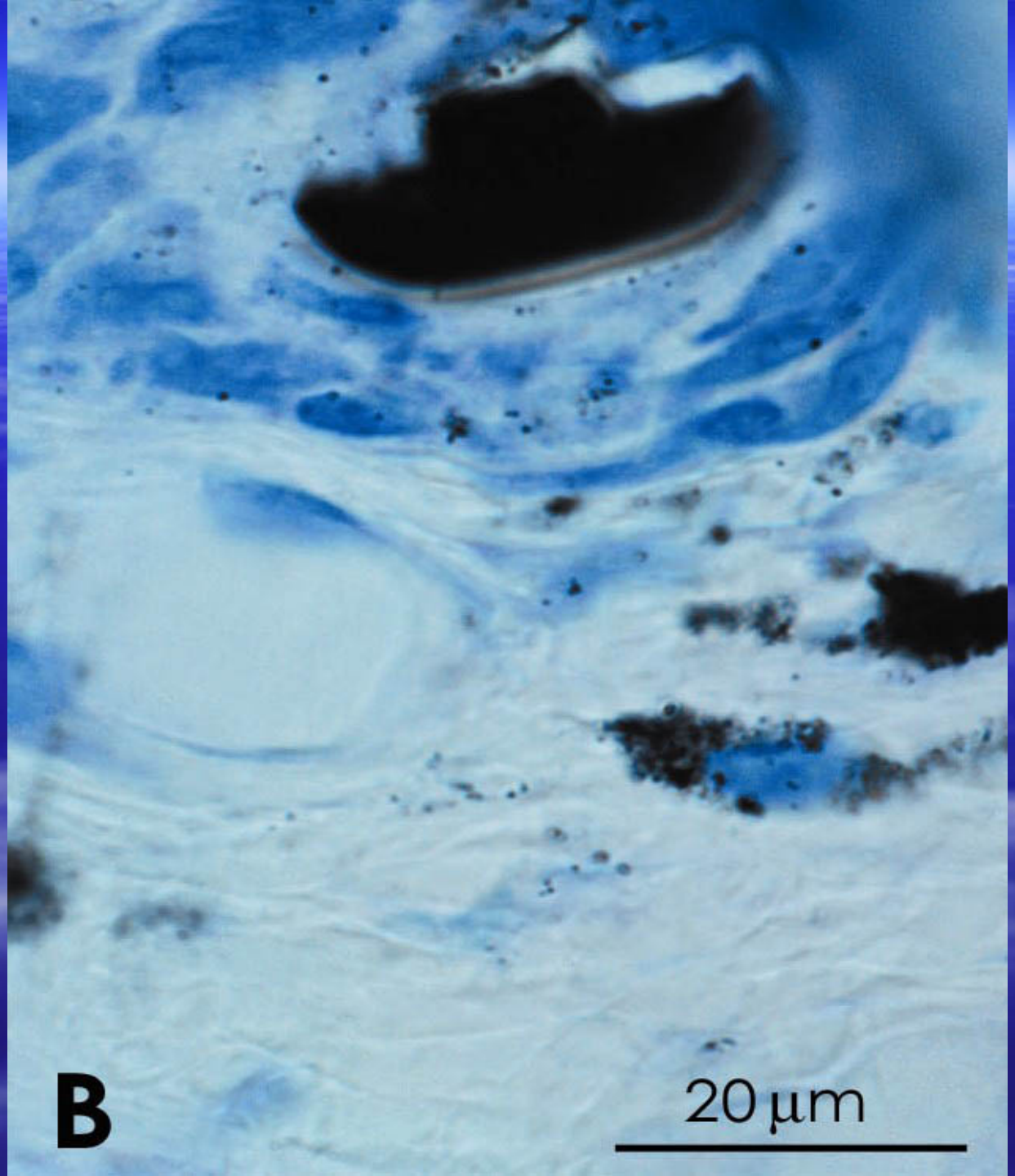

b


dm
cyt
c
nuc

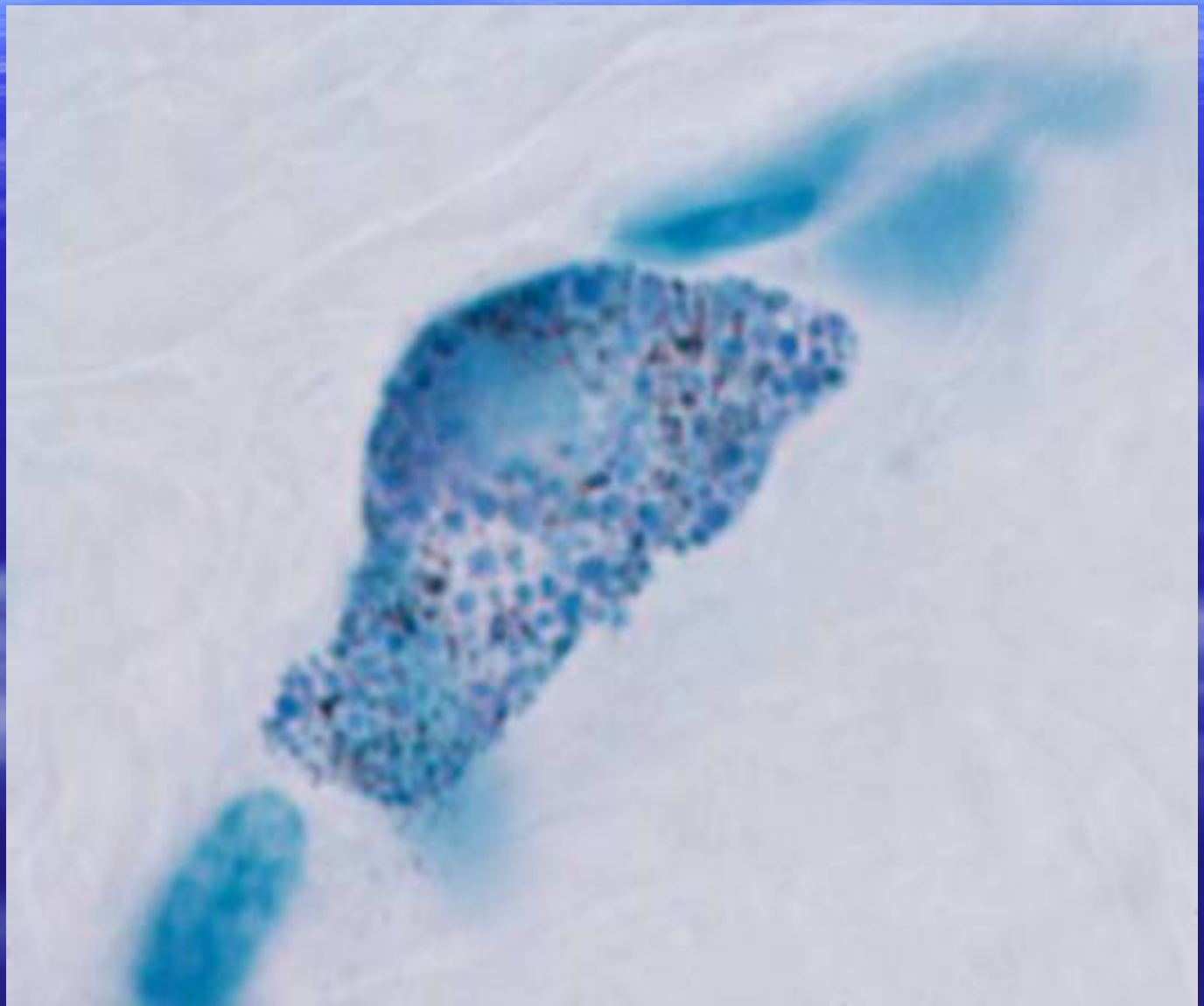
In vivo dissolucytosis

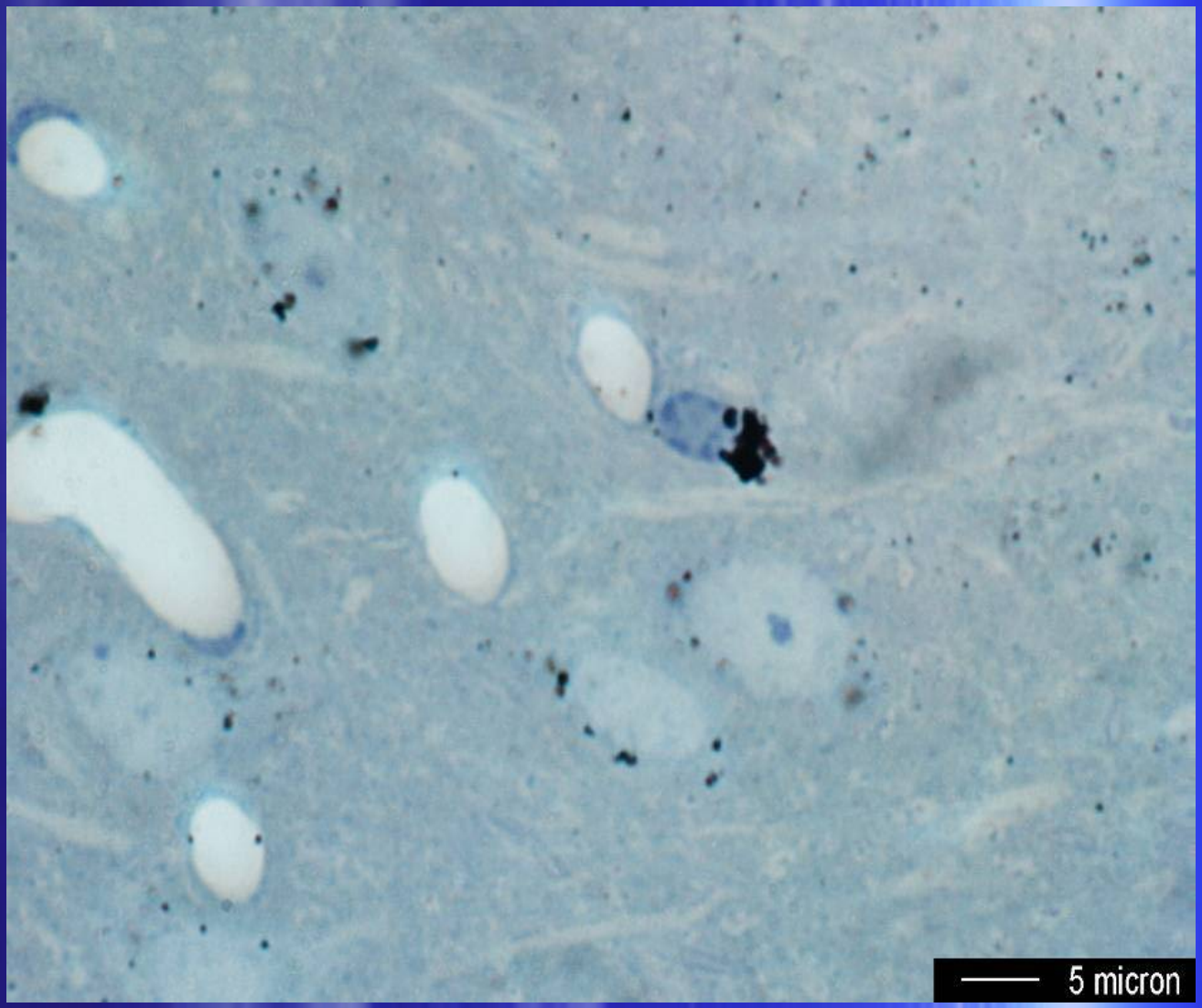
gold implants placed in different organs and tissues cause release of gold ions



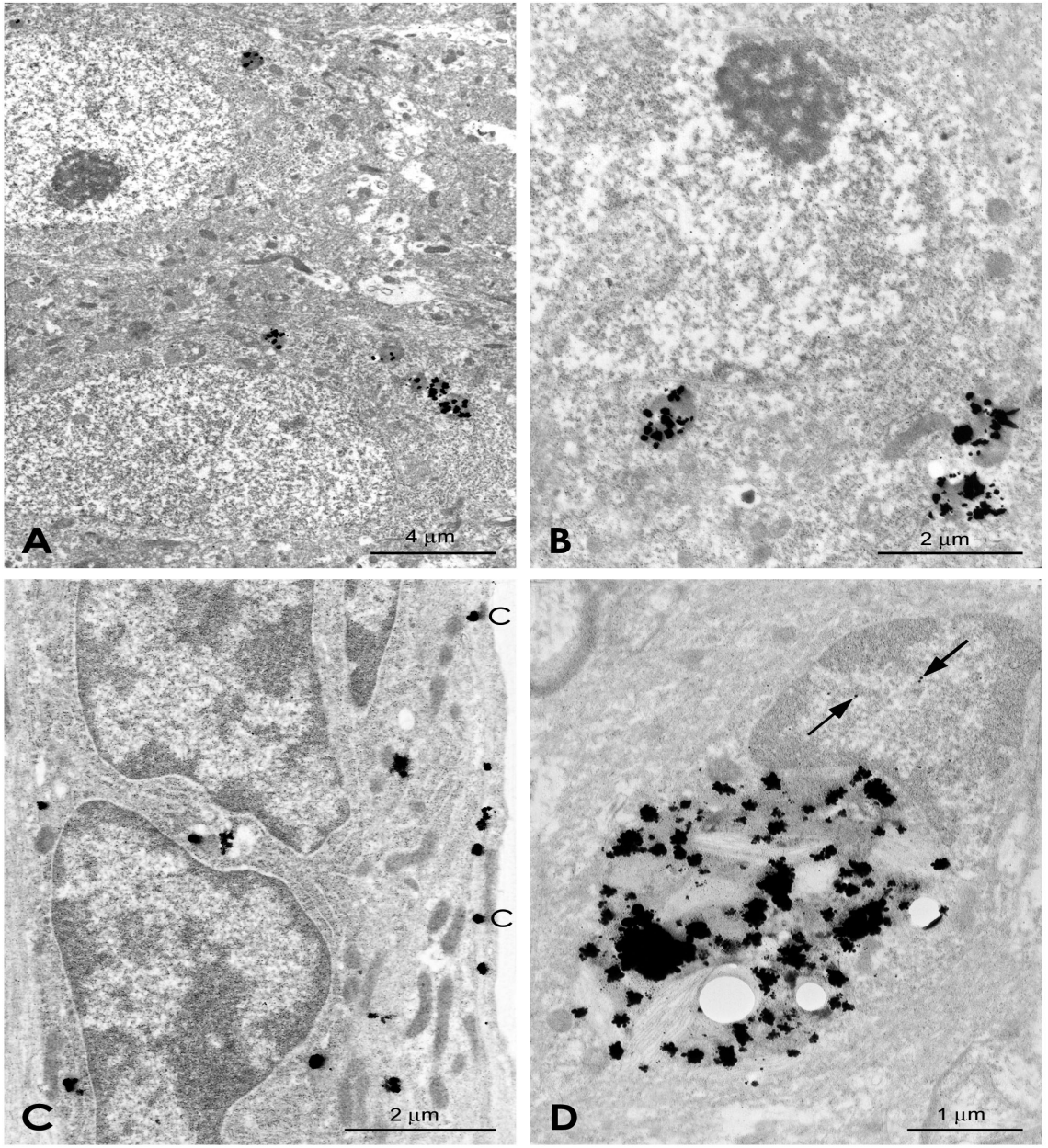

B
20 µm

Mast cell




5 micron

The released gold ions accumulate primarily in lysosomes


A
4 µm
B
2 µm
C
C
C
2 µm
D
1 µm

The gold concept in short

- Gold particles bigger than 20 microns cannot be engulfed by phagocytotic cells
- Instead the phagocytotic cells in casu macrophages change behavior and become dissolucytes that liberate gold ions from the particle surface
- The liberated gold ions are taken up by the dissolucytes themselves and by other cells around the gold particle
- The released gold ions suppress inflammation locally by affecting certain signaling molecules and binding enzyms essentiel for the process

Effect of gold particles on inflammation in the central nervous system

The inflammatory processes seen in the brain generally resembles the processes that take place in other tissues and the brain is thus no longer considered an immunologically privileged organ (Barker & Widner 2004).

Anti-inflammatory effects of metallic gold particles injected into a focal brain injury

We Injected gold particles into mouse brains and made a local Cryo –lesion in the same region. After 14 days the animals were killed

1. a dramatic reduction in the number of activated microglia cells in the damaged tissue

2. a up-regulation of the neuro-protective proteins metallothionine MT(I) and (II).

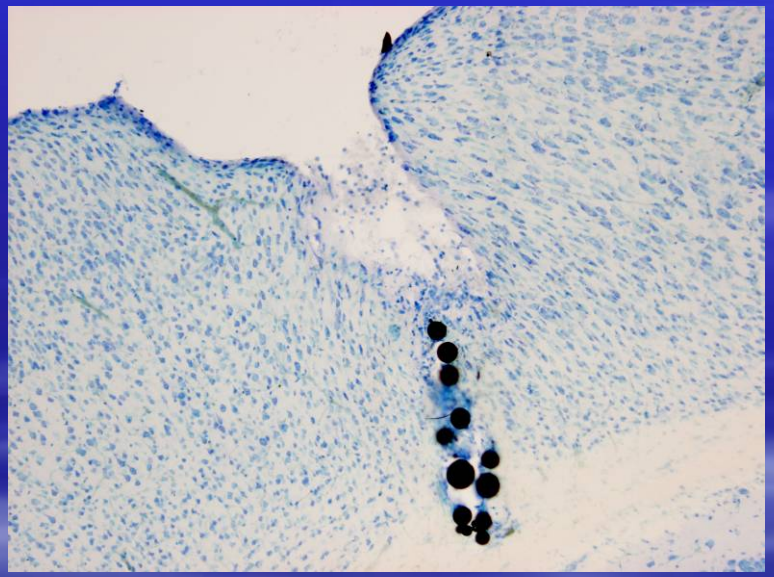
1. an increase in the number of astrocytes

2. a markedly reduced apoptotic activity (Caspase 3 and Tunel)

The anti-inflammatory effects of dissolucytotic released gold ions in CNS signal that metallic gold particles might have interesting clinical potentials in the central nervous system

The gold caused anti- inflammatory and regenerative responses in CNS

- Astroglia ↑
- MT's ↑
- Apoptose ↓
- Microglia ↓



Experimental studies

1. The Effect of Metallic Gold on Wound Healing in C57bl6-mice
2. Effects of Intraarticular gold particles on genetically caused osteoarthritis in Dunkin-Hartly guinea pig
3. Gold treatment of rheumatoid arthritis on a collagene II model
4. The effect of periocular gold particles on autoimmune inflammation in C57BL/6 mouse eye
5. Is the pain reducing effect of gold ions a result of immunosuppresion or of a direct impact on pain perception?

Clinical projects

1. Clinical effects of gold implants on osteoarthritis
2. Clinical studies of pain reducing of gold implants effects on sport related injuries. A pain score analysis
3. Gold caused suppression of autoimmune inflammation in human skin

Closing remarks

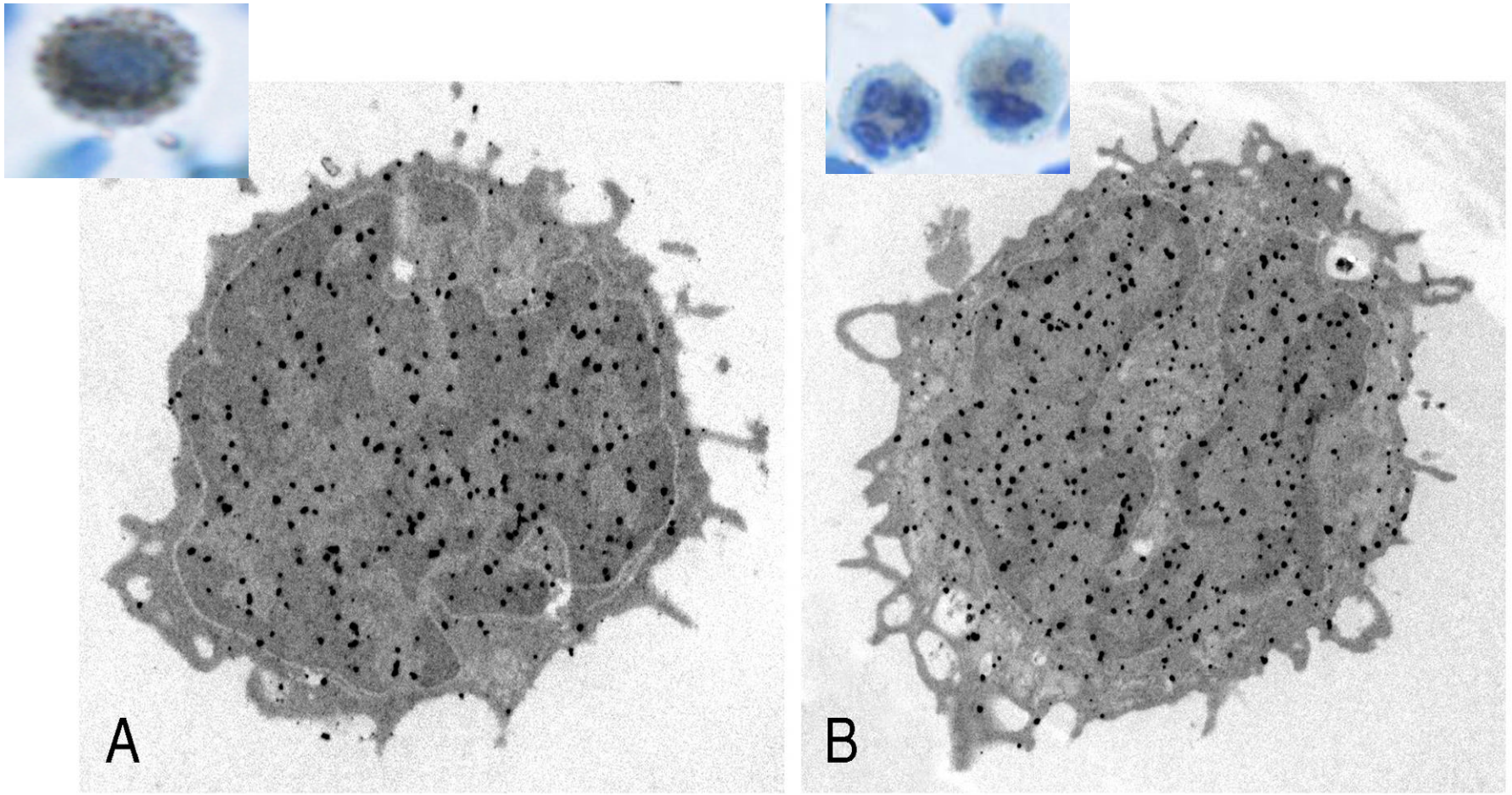
- The amount of released gold ions is dependent of the surface size, i.e. the bigger the surface of a given amount of gold, the more gold ions are released

- We have reasons to speculate that nano-sized intracellular metallic gold units (gold quntum dots/ colloidal gold particles), do not release gold ions

How to tag MTM (membrane translocating molecule) with nanogold

- *A peptide containing the translocation sequence of the tat peptide was bought from Biopetide Co., LLC. The peptide is referred to as tat, and the amino acids correspond to residues 48-57 of the tat protein*
- *0.5 mg Tat was dissolved in 1 ml of distilled water and mixed with 2 ml of a gold quantum dot solution*
- *Buffy coat leucocytes were placed in the MTMq solution for 1 hour before being isolated*
- *After being isolated by centrifugation the cells were fixed in glutaraldehyde (GA), and embedded in plastic*

AMG enhanced gold quantum dots in leukocytes



In conclusion

MTM (membrane translocating molecules) tagged with gold quantum dots can be retrieved with AMG in cells and in tissue sections at light as well as electron microscopical levels.

The AMG approach for visualizing quantum dots is extremely sensitive as dots containing only a few gold atoms can be silver enhance to visible dimensions.

AMG enhanced commercially available quantum dots

CdSe/ZnS Core Shell EviDots (620 nm)

CdSe Core EviDots (618 nm)

Infrared PbS Core EviDots (850nm)