Biological behavior of activated cobalt oxide particles: effect of aging on bioavailability and access to treatments

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Introduction

- Accidental internal contamination of workers with highly radiant submicronic cobalt oxide particles ($^{60}Co_3O_4P$) may occur during procedures such as maintenance
- Due to their poor solubility, $^{60}Co_3O_4P$ may be retained in the lung macrophages for long periods of time, potentially causing pulmonary damage
- Soluble Co species are rapidly eliminated after intake by urinary excretion
- Calcium-trisodium diethylenetriamine-pentaacetic acid (Ca-DTPA) is the recommended treatment following cobalt intake although no proof of efficacy has been reported following inhalation of $^{60}Co_3O_4P$
- By combining the reductant ascorbic acid, to alter the redox state of Co and destabilize the surface of the Co_3O_4P, with a Co chelating agent (DTPA), we aim at increasing the dissolution of Co_3O_4P and thus enhance urinary excretion following accidental intake

Aims:

1. To better understand the relationship between physicochemical properties and biological behavior of Co_3O_4P
2. To provide therapeutic approaches in case of accidental intake

Methods

Particles : Co_3O_4 (Sigma) mean diameter 372 ± 101 nm

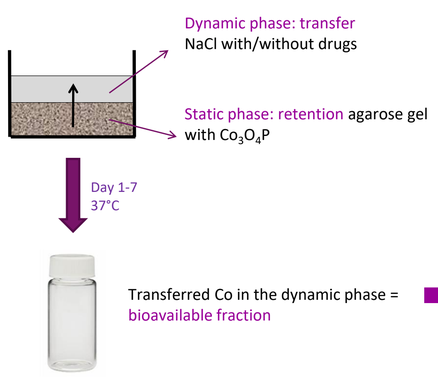
Activation by exposure to external neutron beam
« ISIS »: fast neutrons 500 kW
« ILL »: pure cold neutrons 42 MW

Resulting activated particles contain stable ^{59}Co plus radioactive ^{60}Co and are referred to as $[^{60}Co]Co_3O_4P$

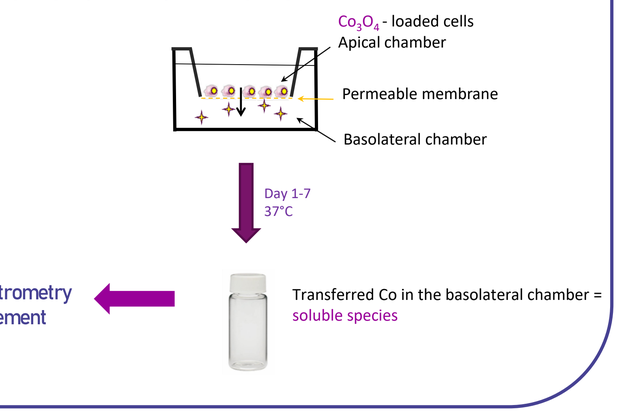
	kBq/mg	^{60}Co/total Co
ISIS particles	12	$3x10^{-7}$
ILL particles	25	$6x10^{-7}$

In vitro models provide information regarding
- Intrinsic dissolution properties of Co_3O_4P according to their activation status
- Activation-induced changes of surface properties (Ascorbate) and availability to chelation (DTPA)

Acellular model: Transfer from a static phase (retention compartment) to a dynamic phase (transfer compartment)



Cellular model: Dissolution of particles following phagocytosis by macrophage-like cells (THP-1)



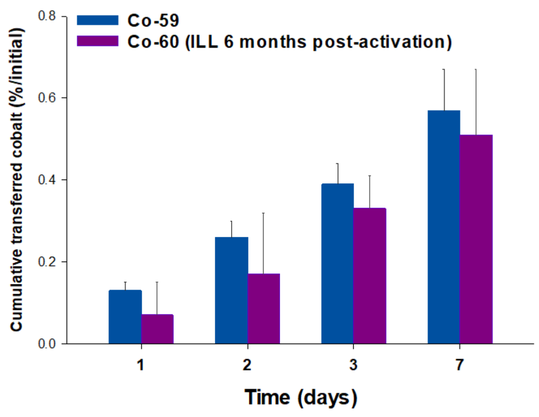
Results

➢ Intrinsic dissolution properties and effect of aging

- Early after activation (within a year), dissolution properties of $[^{60}Co]Co_3O_4P$ evaluated with acellular and cellular models are similar to that of stable particles
- Dissolution from macrophages increases with time post activation

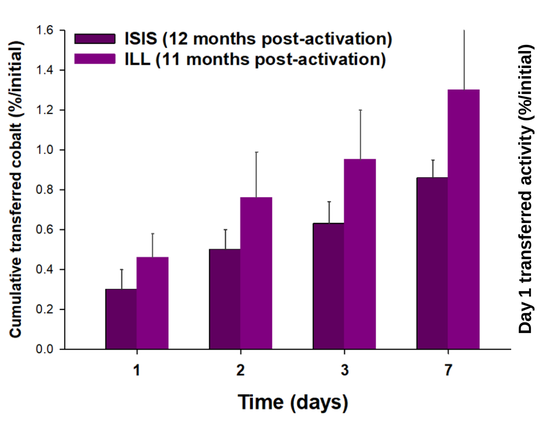
Acellular model

Transfer from static to dynamic phase of soluble Co species

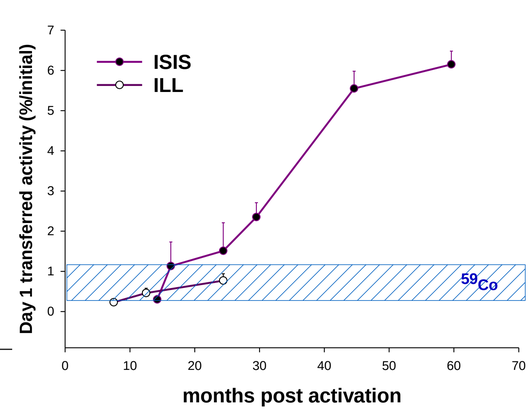


Cellular model

Transfer from apical chamber ($[^{60}Co]Co_3O_4P$ -loaded macrophages) to basolateral chamber of soluble Co species



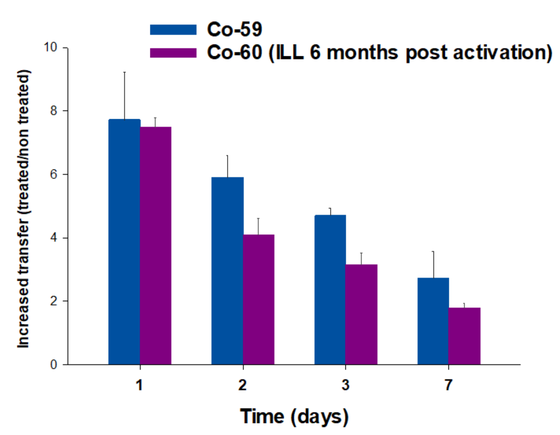
Transfer at Day 1 according to the time post activation of $[^{60}Co]Co_3O_4P$



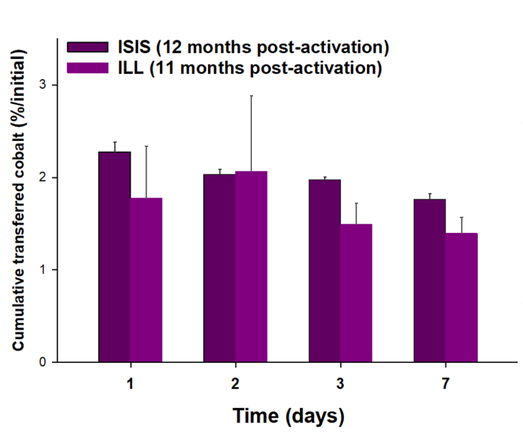
➢ Effect of treatments

- DTPA/Asc increases the dissolution/bioavailability of Co_3O_4P with a similar effect whatever the activation status of the particles
- In acellular model, the enhanced transfer in the presence of DTPA/Asc decreases with the time after incubation whereas in cellular models, the efficacy of treatment is stable over the time of THP-1 incubation
- The effect of treatment decreases sightly differs depending on activation conditions (ISIS versus ILL) and the time post activation

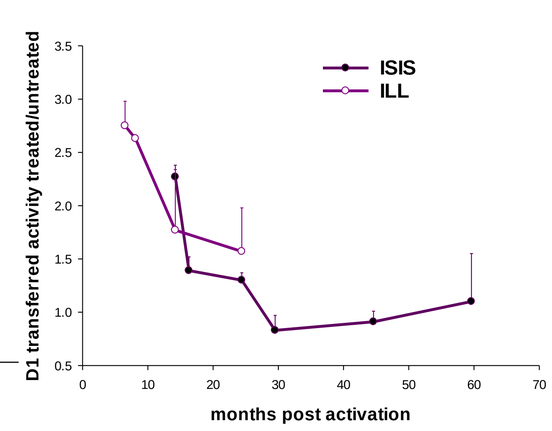
DTPA/Asc induced-transfer from static to dynamic phase as compared to non treated gels



DTPA/Asc induced-transfer from apical to basolateral chamber as compared to non treated cells



DTPA/Asc induced-transfer at Day 1 according to the time post activation of $[^{60}Co]Co_3O_4P$



Conclusions

- Neutron activation seems to modify the dissolution/bioavailability of Co_3O_4 particles with a time-dependent post-activation effect
- DTPA/Asc increases the dissolution/bioavailability of Co_3O_4 particles but the extent to which the treatment is effective may depend on the initial status of the particles (activation and time post-activation)
- *In vivo* rat studies are necessary to evaluate decorporation efficacy of DTPA/Asc following pulmonary intake according to the physicochemical properties of Co_3O_4P

References

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