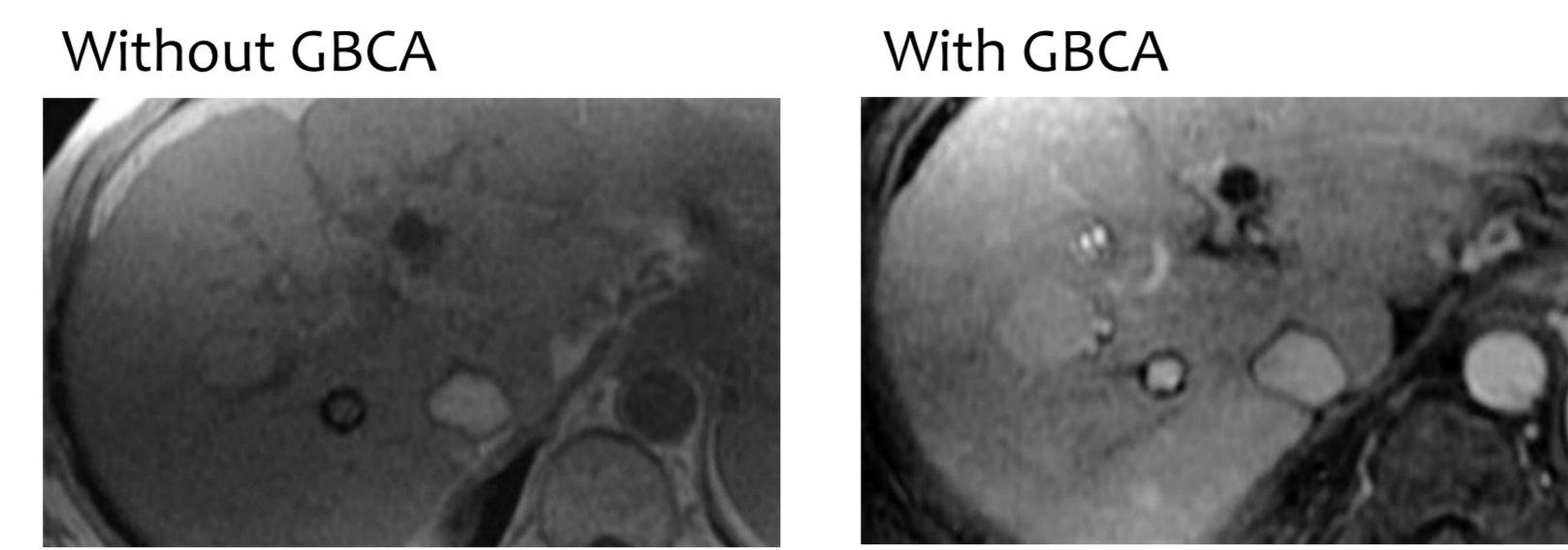
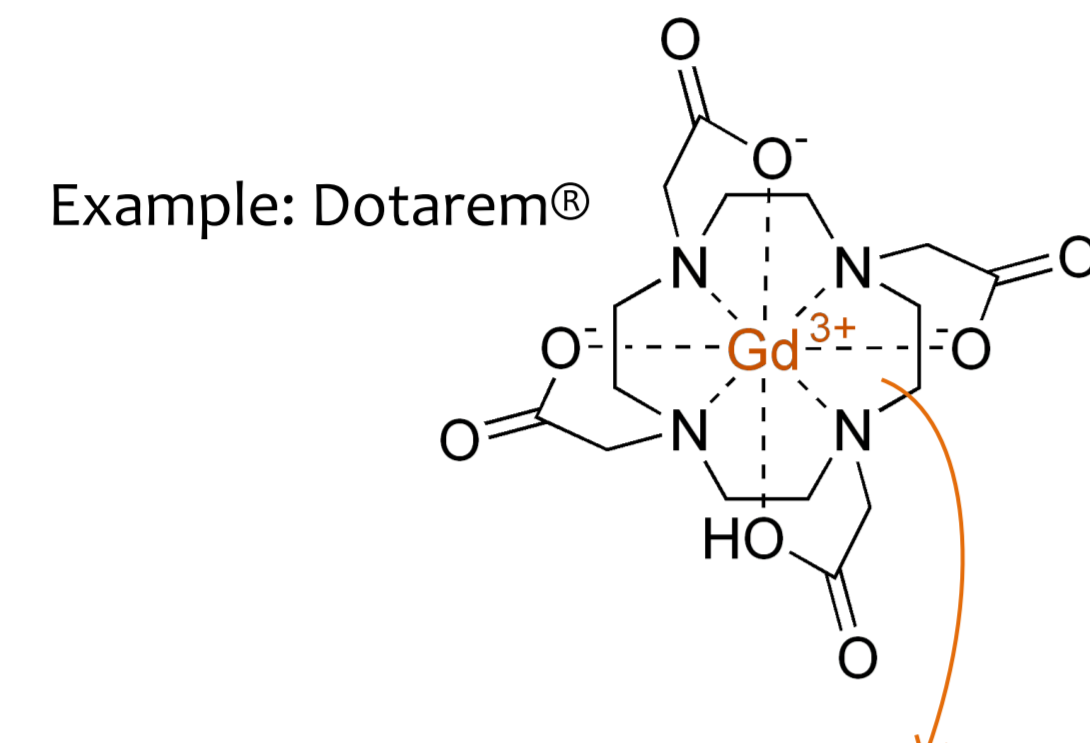


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## Introduction

**Gadolinium-based contrast agents (GBCAs):**  
Currently the only available contrast agents for magnetic resonance imaging (MRI)



Malignant liver lesion: hepatocellular carcinoma (Courtesy of Dr R Schubert, Radiopaedia.org, rID: 15858)

GBCAs (chelators) may partly dissociate and release free  $Gd^{3+}$   
→ ongoing safety concerns: GBCAs linked to nephrogenic fibrosis and deposition in the brain [1]

$Gd^{3+}$  deposition observed in bone several years after administration (at levels much higher than in the brain) [2] → long term storage!

But how is  $Gd^{3+}$  incorporated into bone?

- Organic phase of bone?
- $GdPO_4$  (known to be insoluble in physiological medium [3])?
- $Gd$ -substituted bone mineral (hydroxyapatite)?

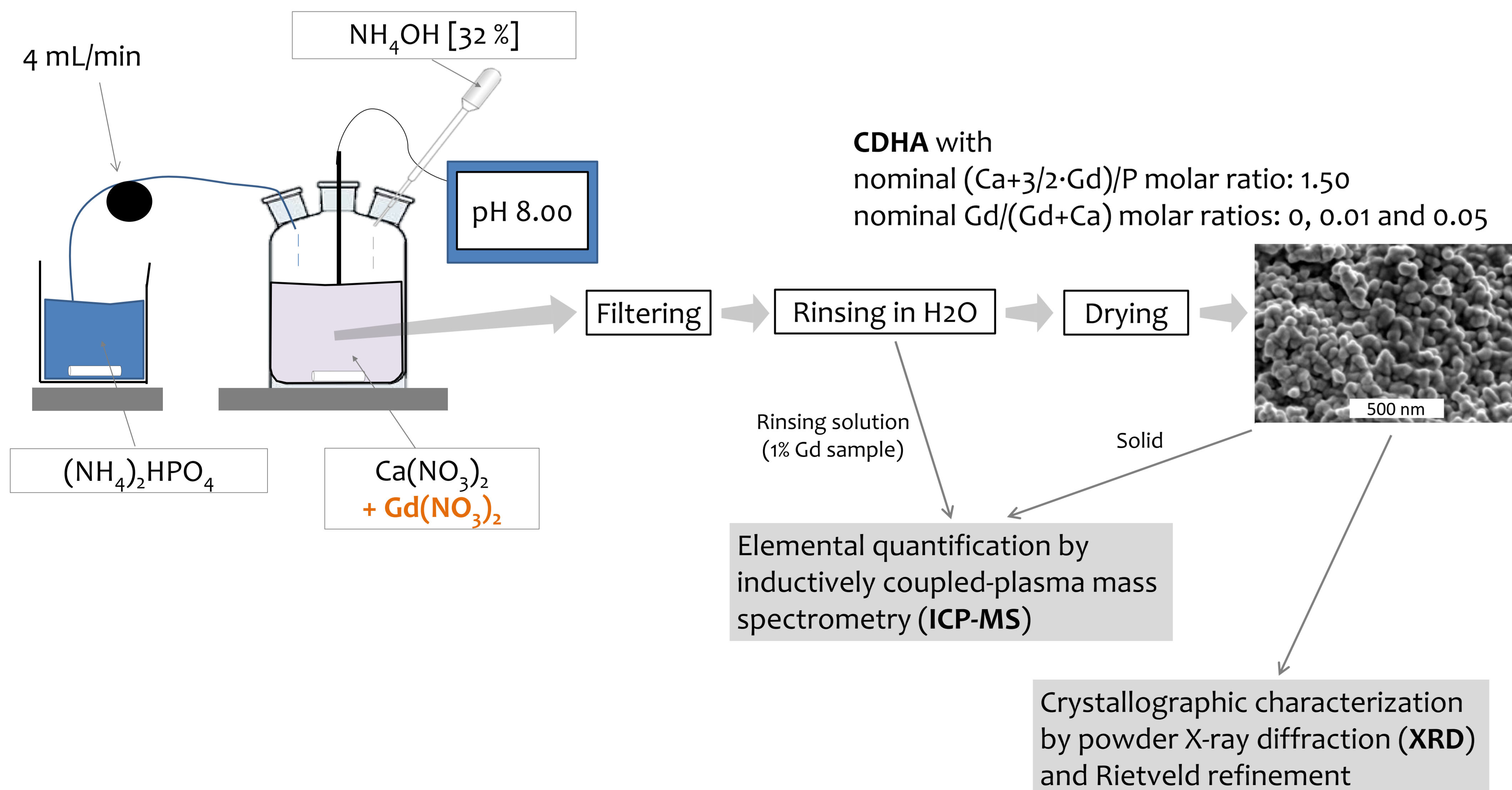


**Goal of the present work:**

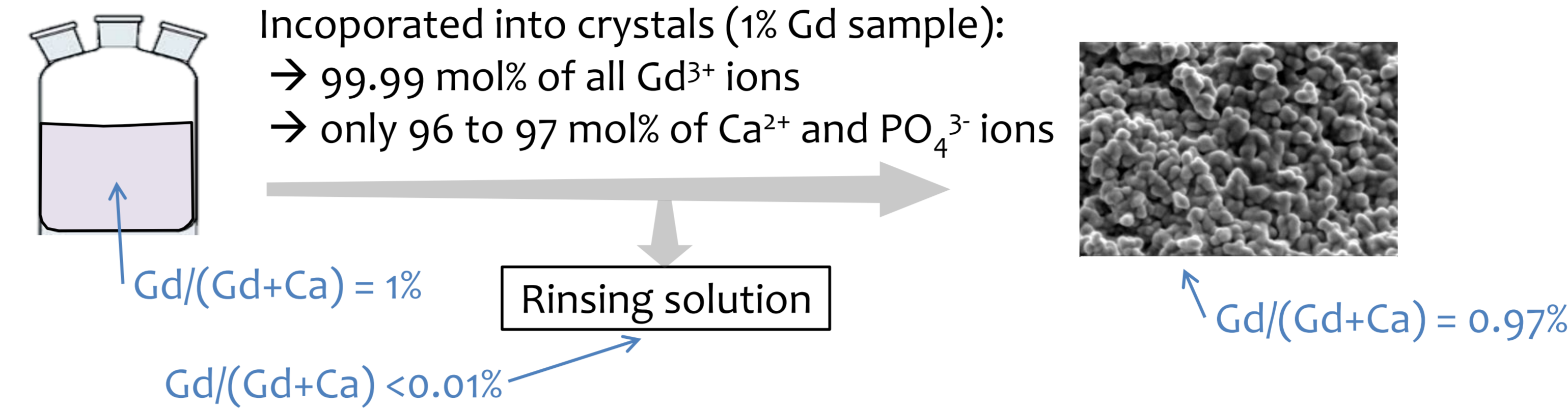
To investigate whether  $Gd^{3+}$  precipitated along with  $Ca^{2+}$  and  $PO_4^{3-}$  from a supersaturated solution is incorporated into the crystal structure of a bone-like calcium phosphate phase

## Method

Precipitation of calcium deficient hydroxyapatite (CDHA)



## Results & Discussion

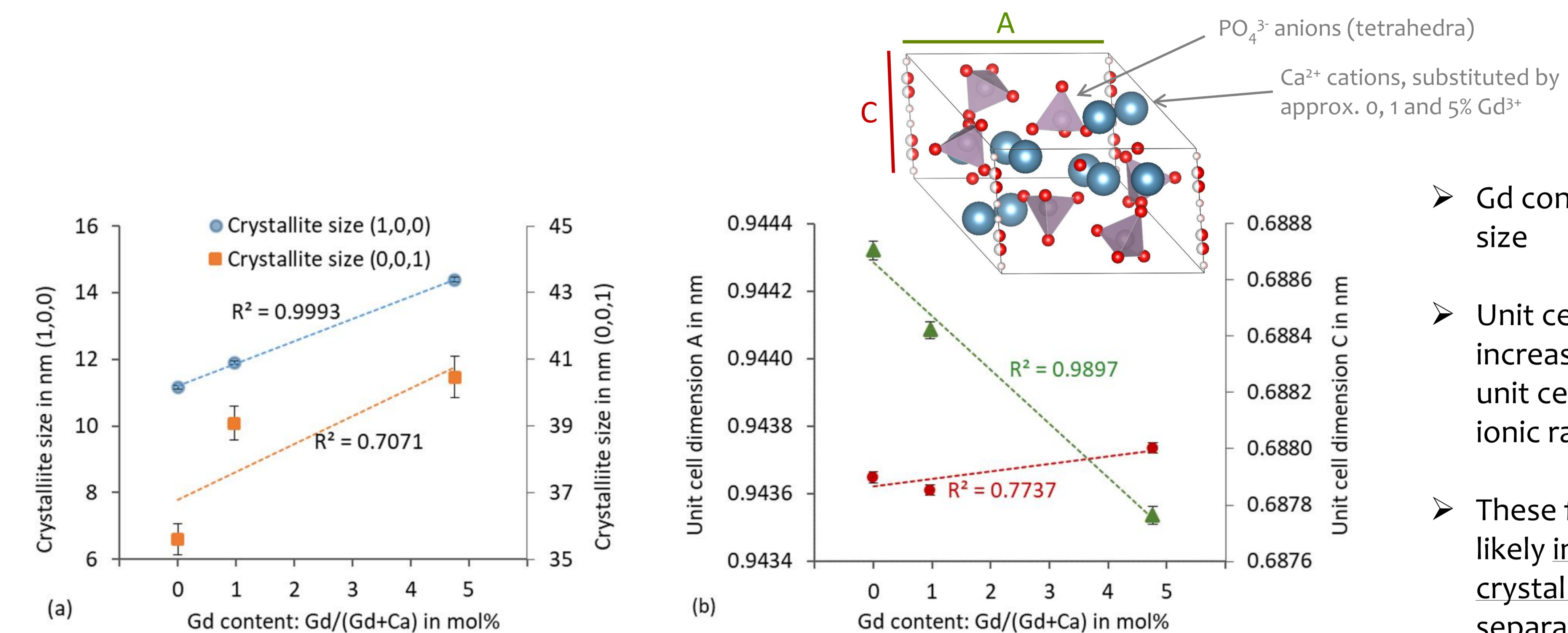


$Gd^{3+}$  is highly insoluble and was permanently incorporated into the precipitated crystals

Chemical and crystallographic parameters of the  $Gd$ -containing precipitate

$Gd / (Gd+Ca)$ nominal in mol%	$Gd / (Gd+Ca)$ (ICP-MS) in mol%	Phases detected (XRD)	Amorphous fraction (XRD) in wt%
0%	0%	CDHA	14%
1%	0.97%	CDHA	14%
5%	4.76%	CDHA	19%

The precipitate consisted of phase-pure CDHA with a  $Gd$  content close to nominal quantities, and accompanied by an amorphous fraction of <20 wt%



Crystallite size (a) and unit cell dimensions (b) of the CDHA crystal lattice as a function of  $Gd$  content. Error bars designate the estimated standard deviation associated with the Rietveld refinement.

- $Gd$  content affects the CDHA crystallite size
- Unit cell dimension  $A$  decreases with increasing  $Gd$  content → a contracted unit cell is in line with the smaller  $Gd^{3+}$  ionic radius compared to  $Ca^{2+}$  [4]
- These findings imply that  $Gd^{3+}$  was most likely incorporated into the apatite crystal lattice rather than forming a separate  $GdPO_4$  phase

## Conclusions

- Chemical and crystallographic analysis of the precipitate formed from a supersaturated solution of  $Gd^{3+}$ ,  $Ca^{2+}$  and  $PO_4^{3-}$  provided strong evidence of a  $Gd$ -containing apatite crystal structure
- Thus,  $Gd^{3+}$  ions dissociated from their chelators *in vivo* after GBCA administration may be directly incorporated into the mineral phase of bone during bone formation or remodeling

## References

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