In vivo cell tracking with $^{52}$Mn PET: Targetry, Separation, and Applications

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Introduction

$^{52}$Mn ($t_{1/2} = 5.59$ d, $\beta^+ = 29.6\%$, $E_{\beta_{\text{max}}} = 0.58$ MeV) has great potential as a long lived PET isotope for use in cell tracking studies, observation of immunologic response to disease states, or as an alternative to manganese-based MRI contrast agents. Its favorable max positron energy leads to superb imaging resolution, comparable to that of $^{18}$F.[1]

Manganese is naturally taken up by cells via a multitude of pathways including the divalent metal transporter (DMT1), ZIP8, transferrin receptors (TfR), store-operated Ca$^{2+}$ channels (SOC-Ca$^{2+}$), and ionotropic glutamate receptor Ca$^{2+}$ channels (GluR).[2] These natural transport mechanisms make $^{52}$Mn an attractive isotope for applications necessitating non-perturbative cell uptake. In particular, cell tracking is critical to the development and translation of stem cell therapies in regenerative medicine. Alternatively, $^{52}$Mn could be used in immunotherapy techniques such as adoptive cellular therapy (ACT) to evaluate the ability of external immune cells to reach their intended target.

Material and Methods

$^{52}$Mn was produced by natCr(p,x)$^{52}$Mn using 16 MeV protons. The average thick target production yield was 0.23 mCi/µA-h with less than 0.25% co-production of $^{54}$Mn. Small amounts of $^{51}$Cr were observed in the target, but were absent from the radiochemically separated product.

Target construction consisted of a water jet cooled chromium disc (3/4” diameter, 0.4” thick). Targets were purchased from Kamis Inc, and are 99.95% pure. Targets withstood beam currents of 30 µA with no visible aberration.

Chromium targets were etched by concentrated HCl following bombardment. Mn$^{2+}$ ions were extracted from 9M HCl to 0.8M trioctylamine in cyclohexane leaving the bulk chromium in the aqueous phase. After isolating the organic phase, 0.001M NH$_2$OH was used to back-extract the Mn$^{2+}$ ions to aqueous phase. This purification cycle was conducted a total of three times for each $^{52}$Mn production.

Results and Conclusion

For a starting bulk chromium mass of 456 ± 1 mg, a post-separation chromium mass of 5.35 ± 0.04 ng was measured by microwave plasma atomic emission spectrometry (MP-AES). This mass reduction corresponds to an average separation factor of 440 for a single purification cycle. Each purification cycle had a $^{52}$Mn recovery efficiency of 73 ± 7% (n = 6), resulting in an overall separation efficiency of approximately 35%. These efficiencies and separation factors agree reasonably well with the work conducted by Lahiri et. al.[3] Prior to use, the product was passed through a C-18 Sep-Pak to remove any residual organic phase.

After four target irradiations and etchings, some pitting became noticeable on the target face. These have not yet compromised the o-ring seal with the target deplater, but it is possible that target replacement after every 6–9 $^{52}$Mn productions will be necessary moving forward.

Following the successful separation of $^{52}$Mn from chromium, in vitro experiments were conducted to demonstrate the uptake of $^{52}$Mn by human stem cells and mouse tumor cells. A linear uptake response was observed as a function of the amount of activity exposed to the cells for both cell models. These experiments have shown great promise for $^{52}$Mn as a long-lived PET isotope in cell tracking studies. Details will be presented.

References


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