

Utility of MALDI Imaging Mass Spectrometry in Drug Discovery: Histological Distribution of Chloroquine and Its Metabolite(s) in The Ocular Tissue of Pigmented Rats

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PURPOSE

We previously reported that the histological distribution of chloroquine in the retina, ocular melanin-containing tissue, of pigmented rats using matrix-assisted laser desorption/ionization (MALDI)-imaging quadrupole time-of-flight (Q-TOF) mass spectrometry (MS).^{Ref)} The purpose of this study was to examine the histological distribution image of chloroquine and its metabolite(s) simultaneously obtained in this application in the retina of pigmented rats: the quantitative aspects and reproducibility were verified.

INTRODUCTION

MALDI-imaging MS has emerged as a new technique for drug discovery and development by several pharmaceutical companies. MALDI-imaging MS combines the benefits of both ARG and LC-MS/MS, and is capable of mapping the non-radiolabeled distribution of both the parent drug and its metabolites using visual-spatial images. This has allowed the relationship between efficacy or toxicity with drug concentration to be evaluated in greater detail and at lower cost than ARG and LC-MS/MS combined, thereby providing a powerful addition to the toolbox for the spatial analysis of tissue distribution in drug discovery.

METHODS

At 24 h after single oral administration of chloroquine to pigmented rats, 10- μ m sections taken from the single eyeball of each rat were prepared. The tissue sections were sprayed with MALDI Matrix CHCA using an automated sprayer, and analyzed using a Q-TOF MS equipped with MALDI source. The other eyeball was used for determining the concentrations of chloroquine by HPLC. The eyeball was solved in soluen-350 (Perkin Elmer), and then an aliquot of the sample was subjected to HPLC (Alliance 2695 HPLC system, Waters).

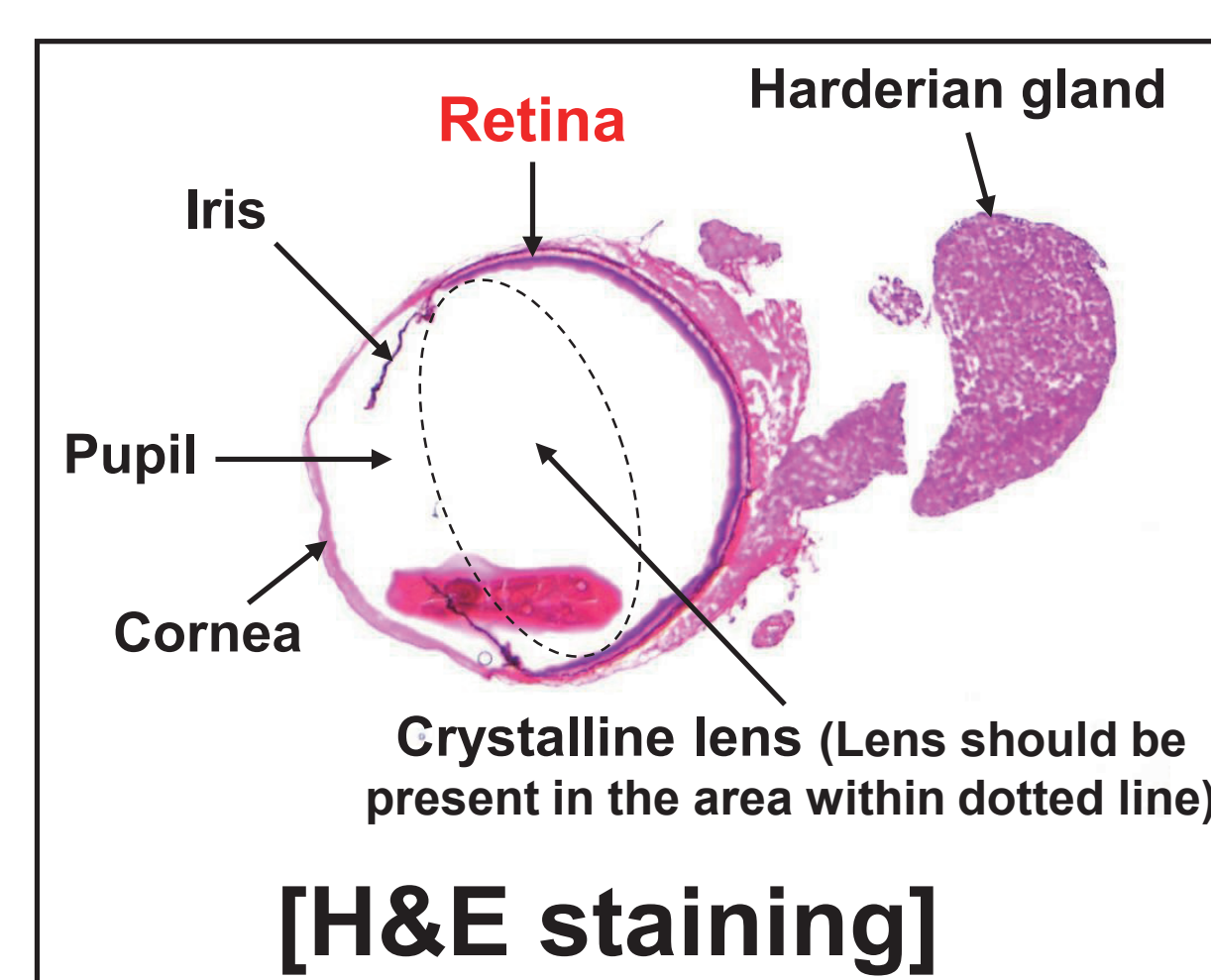
MS condition for only chloroquine :

Q m/z 320.18, product m/z 247.1 was used for imaging

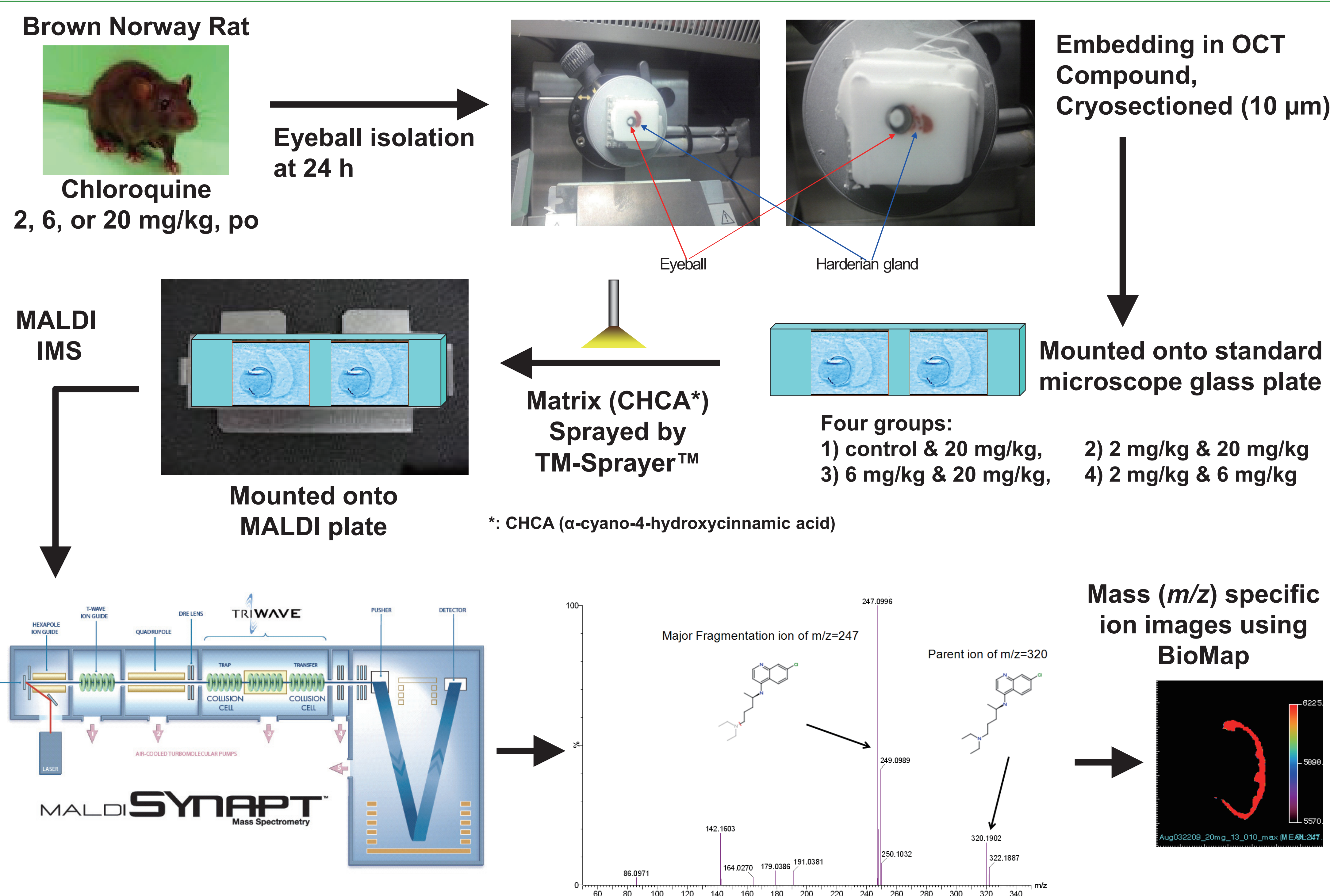
MS condition for both chloroquine and n-desethylchloroquine :

Q m/z 320.18, product m/z 142.15 was used for imaging

Q m/z 292.18, product m/z 114.12 was used for imaging

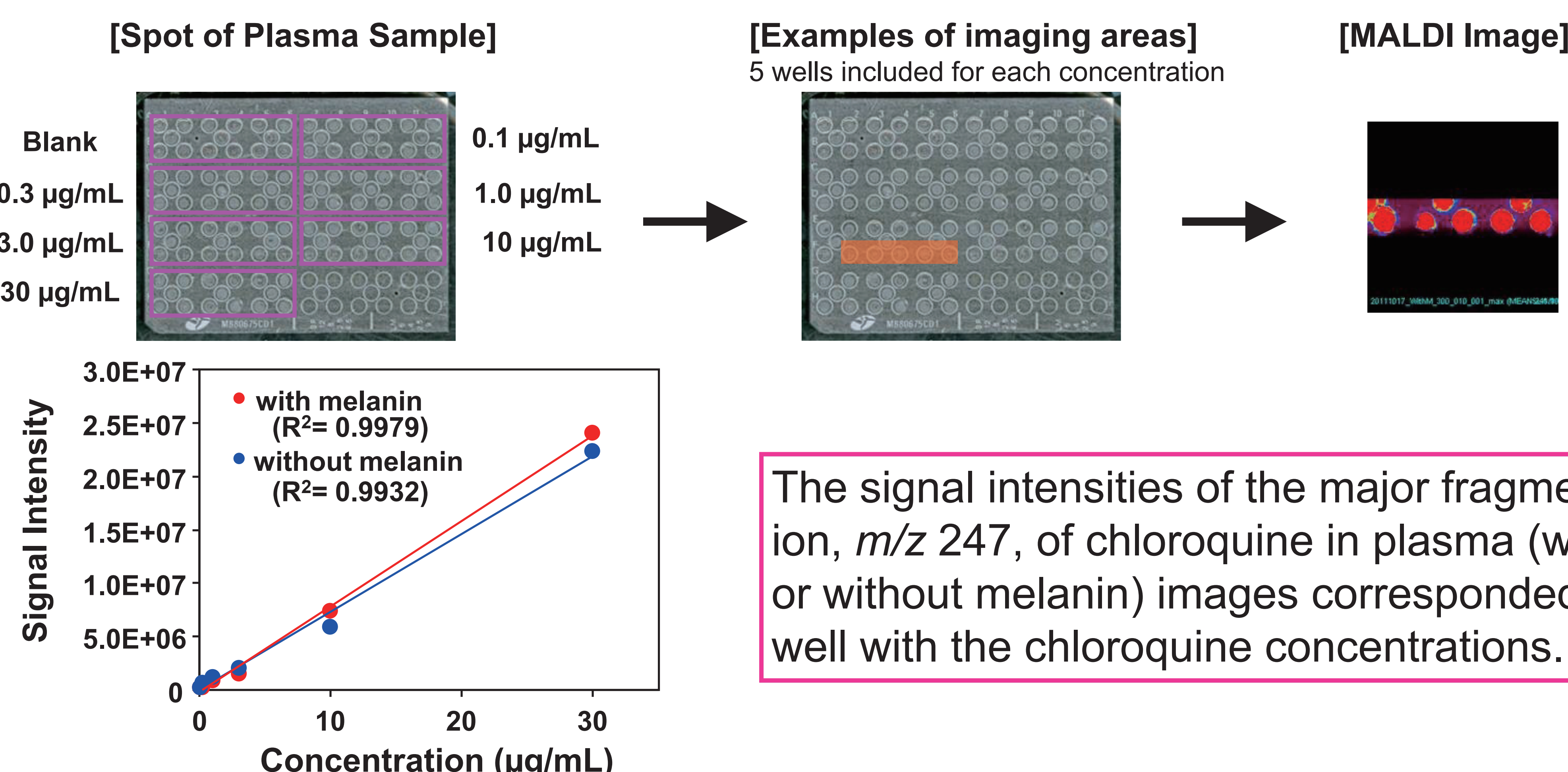


MALDI Imaging MS Process for Rat Eyeball Sections

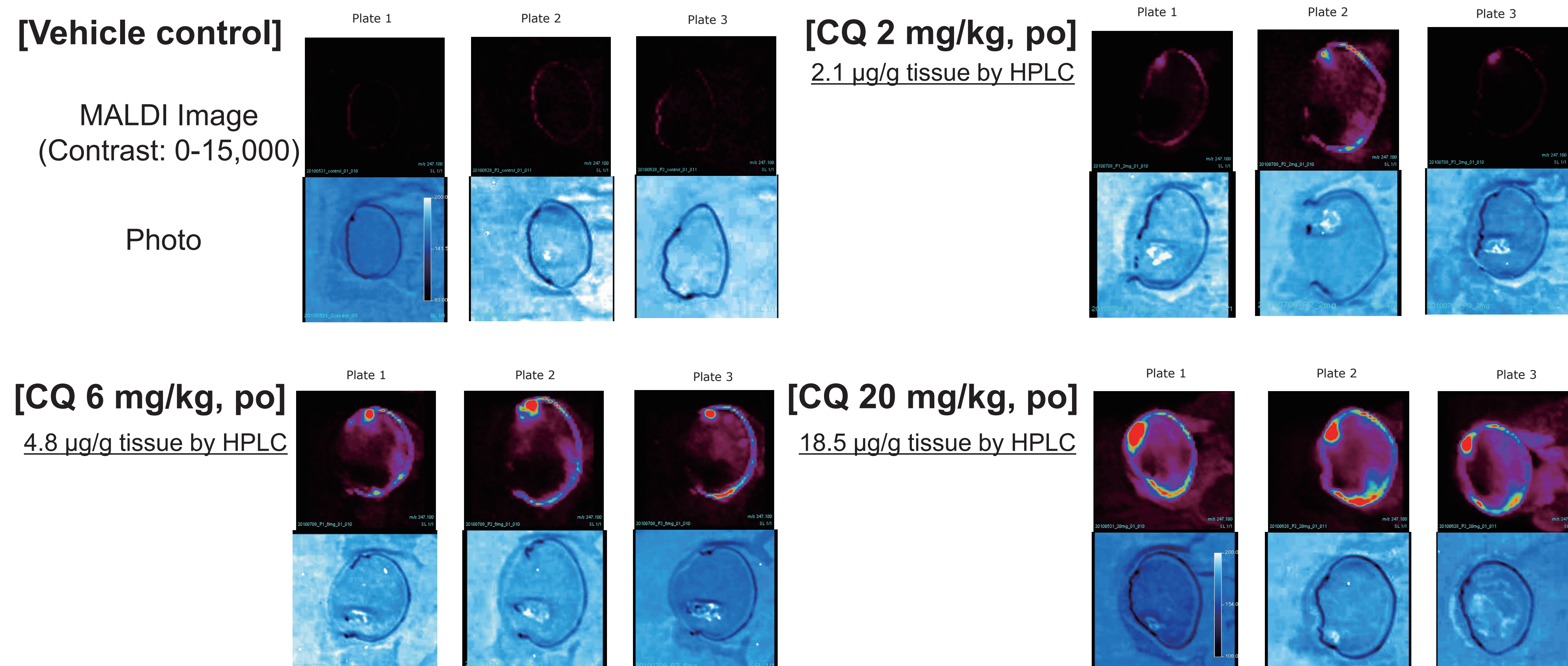


RESULTS

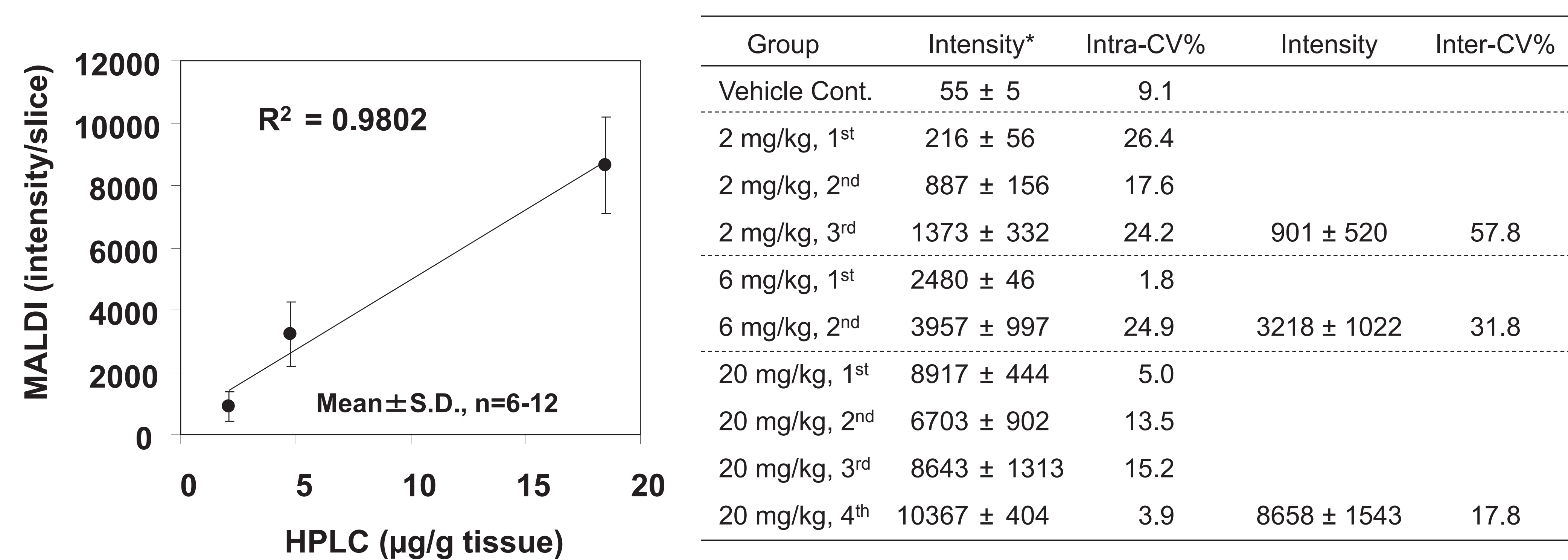
Quantitative Aspects of Chloroquine in Rat Plasma by MALDI Imaging MS



Localizing Chloroquine in Pigmented Rat Eyeball



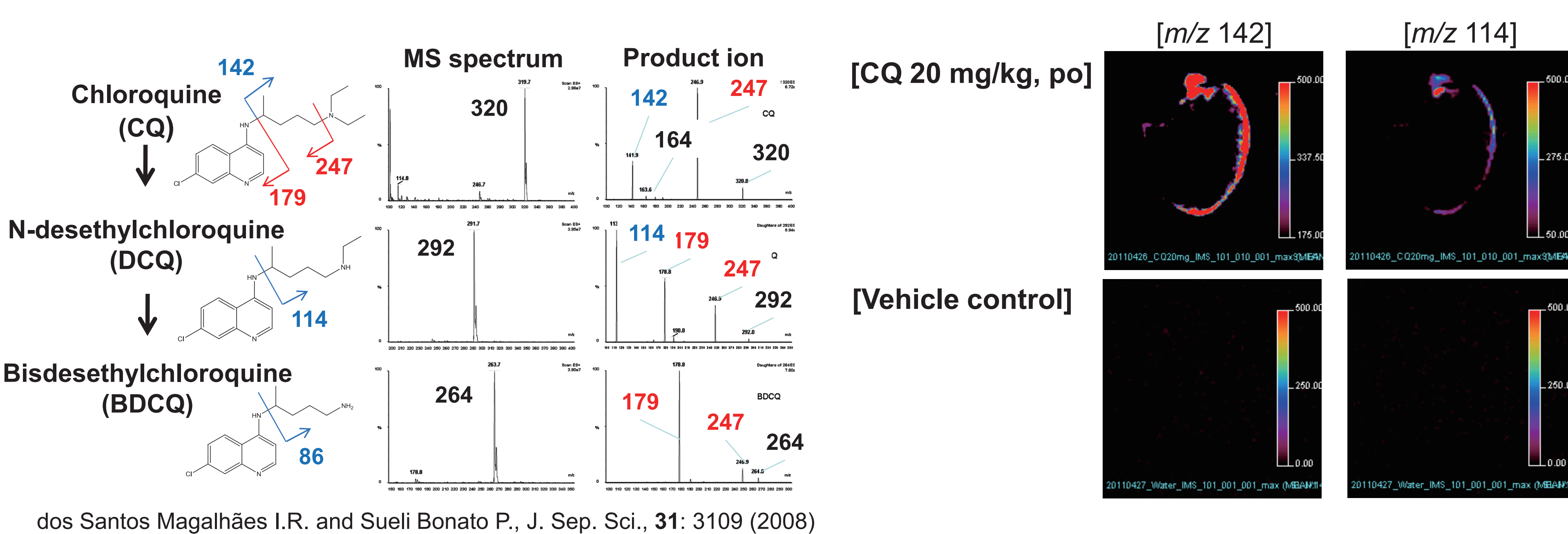
Correlation of MALDI and HPLC Data for Chloroquine in Rat Eyeball



*: Each value represents the mean \pm S.D. of triplicate determinations.

The signal intensities of the major fragment ion, m/z 247, of chloroquine within the retina in distribution images corresponded well with the chloroquine concentrations in ocular tissues measured by HPLC.

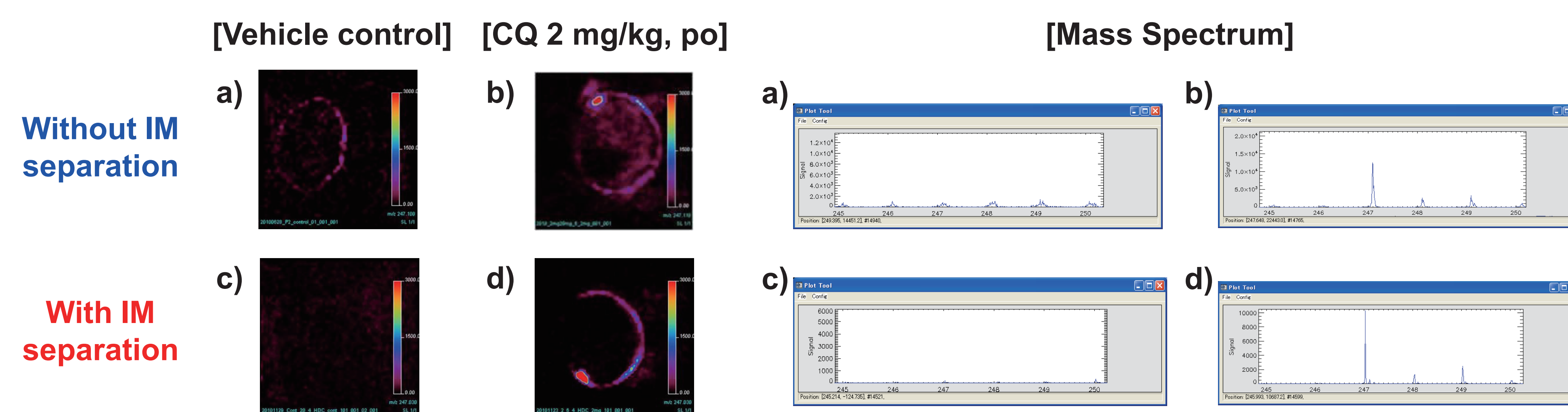
Localizing Chloroquine and Its Metabolite in Pigmented Rat Eyeball



• Chloroquine and one of its metabolites, n-desethylchloroquine, were detected in the MS/MS mode by monitoring of their specific fragment ions, m/z 142 and 114, respectively, and imaged through the rat eyeball.

• The distribution of the metabolite was similar to that observed for chloroquine in terms of the histological images and specific localization to retina.

Application of Ion Mobility (IM) Separation for MALDI Imaging MS



Ion mobility separation effectively reduced the background signals.

CONCLUSIONS

- Chloroquine and n-desethylchloroquine were simultaneously analyzed by MALDI imaging MS: the quantitative aspects and reproducibility of the specific localization of chloroquine were verified.
- The distribution of the metabolite was similar to that observed for chloroquine in terms of the histological images and specific localization to retina.
- This technology can provide relevant information concerning the molecular mechanisms underlying drug efficacy and/or safety in drug discovery.