Synthesis of stereochemically pure $^{18}$F-cis-4-fluoro-L-proline on an automated synthesis module.

Alexander Schmitz$^1$, Richard Freifelder$^1$

$^1$University of Pennsylvania, Dept. of Radiology, 3400 Spruce St., Philadelphia, PA 19128, USA

**Objectives:** $^{18}$F-cis-4-fluoro-L-proline is a radiotracer used to image pulmonary fibrosis. It was requested for animal PET scans by researches at Penn. The goal was to develop a method to synthesize stereochemically pure $^{18}$F-Proline on an automated synthesis unit with minimum changes to existing commercially available kits. For this purpose we used our IBA Synthera unit, which was originally designed for the cGMP compliant manufacture of FDG.

**Methods:** Based on manual test runs a synthesis script was written by varying the reaction parameters such as: temperature, heating time, and concentration of certain reagents and tested with multiple synthesis runs. In general $^{18}$F is collected from an irradiated $^{18}$O water target on a QMA cartridge, eluted with Kryptofix2.2.2/carbonate and evaporated to dryness. The precursor N-Boc-trans-4-tosyloxy-L-proline methyl ester is added to the reaction vial. After hydrolysis the product is collected and reference standards for $^{18}$F-cis-4-fluoro-L-proline and its diastereomere were used to identify the desired radiotracer and stereochemical purity of the final product using HPLC.

**Results:** Stereochemically pure $^{18}$F-cis-4-fluoro-L-proline was successfully synthesized on our automated synthesis module. We were able to adapt and develop a synthesis method with minor changes to commercially available cassettes and supplies. The resulting automated production runs for these radiotracers showed a decay corrected yield of 15% on average and stereochemical and chemical purity of 99%, no semi-prep HPLC was needed for purification Commercially available synthesis disposables (cassettes) without hardware modifications were used for all experiments. The tracer was then used by the requesting researchers in our animal scan facility.

**Conclusion:** This automated synthesis unit offers a convenient and reliable way to synthesize $^{18}$F-cis-4-fluoro-L-proline under remote conditions. Advantages of this automated process in comparison to previously published methods are cGMP compliant set-up, improved yields, reliability and stereochemical purity.

<table>
<thead>
<tr>
<th>Production runs</th>
<th>Synthesis Time [min]</th>
<th>Average yield [d.c.%]</th>
<th>Stereochemical purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F-cis-Proline</td>
<td>8</td>
<td>75</td>
<td>14.6</td>
</tr>
</tbody>
</table>
$\text{[18F]}\text{KF/Cryptand 2.2.2}$

MeCN, 90°C

0.1n HCl
120°C

1n NaOH
RT