BG75 Plus [^{11}C] Upgrade – CPM and Target

Automated [^{11}C]Acetate Production & QC

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I. SUMMARY:

This white paper describes the latest developments from ABT R&D on the BG75 Plus system. The BG75 Plus system is a [^{11}C] capable radio-isotope generator (RIG) and a [^{11}C] Chemistry Production Module (CPM) and [^{11}C]Acetate dose synthesis card (DSC) developed in conjunction with the Athinola A. Martinos Center at Massachusetts General Hospital.

II. BACKGROUND:

The vision of the Dose on Demand® Biomarker Generator system was to be able to produce [^{18}F] and [^{11}C] interchangeably. With recent developments in the RIG 2.0[1], the BG75 system is now [^{11}C] capable. To this end, ABT R&D has developed a prototype [^{11}C] target with expected production numbers of 300-600 [mCi] of [^{11}C] in 20 [min]. A [^{11}C] CPM and [^{11}C] Acetate DSC are in development with the Martinos Center for preclinical injection and eventually clinical injection.

III. CPM ARCHITECTURE:

The architecture of the [^{11}C] CPM is shown in Figure 1. The system has been designed with [^{11}C] Acetate in mind.

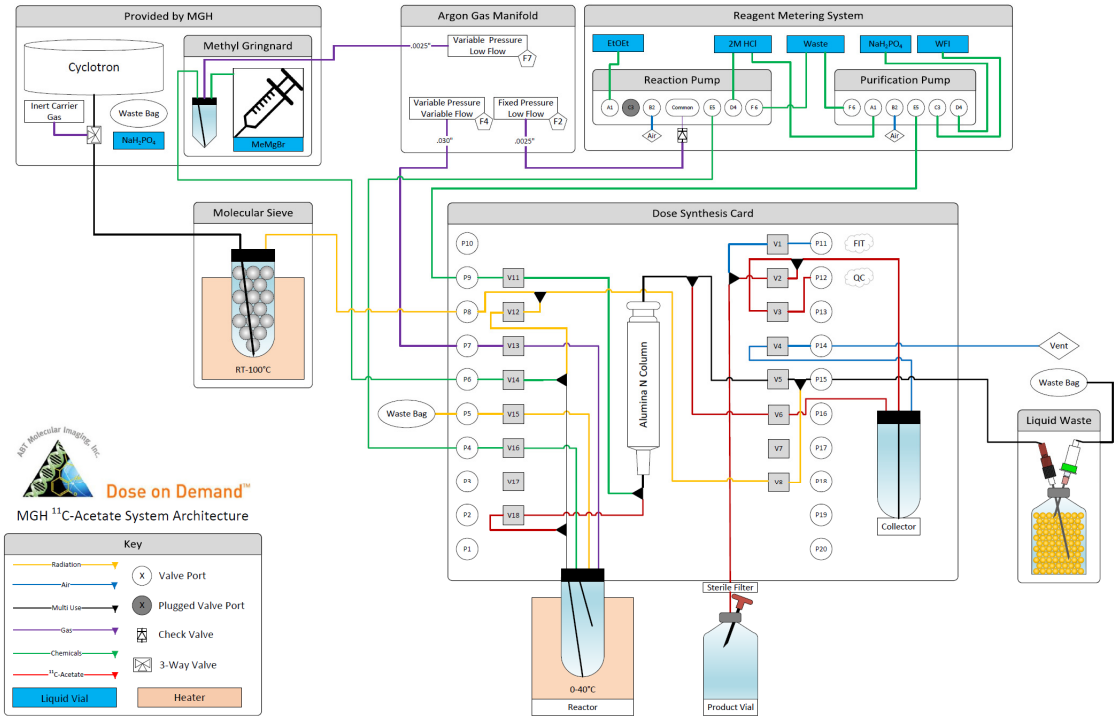

Figure 1. [11C]Acetate CPM and DSC design using methyl grignard.

IV. Function:

The sections below describe the development efforts of the [^{11}C] RIG and target along with the CPM and DSC.

BG75 Plus [^{11}C] RIG and Target

The prototype [^{11}C] target is shown in Figure 2. The target will be a N_2 gas target which will withstand up to 30 [uA] of p^+, proton beam current. The chamber of the target was designed based on optimizing the tradeoff between energy deposition and cooling in conjunction with Bruce Technologies, Inc.

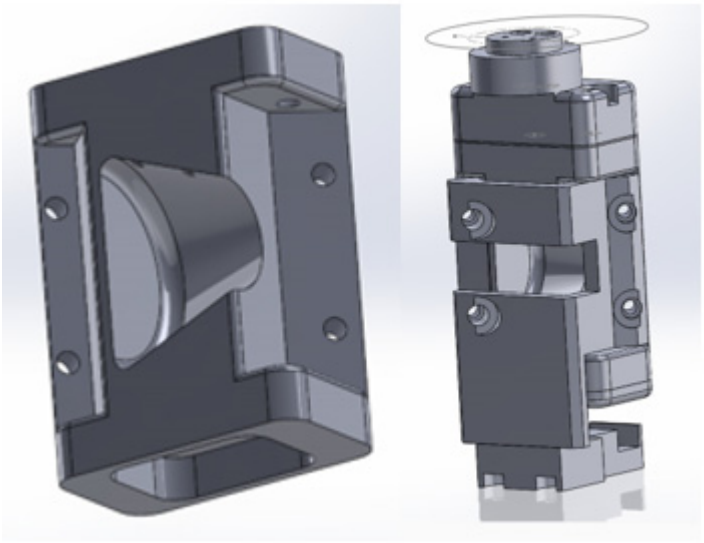

Figure 2. Prototype target for [^{11}C] production in BG75 Plus system. The chamber has been optimized to capture as much beam energy deposition as possible.

Figure 3 illustrates thermal simulations on the beam collimator used to reduce thermal heating of the side window of the target. The simulations were performed in COMSOL.

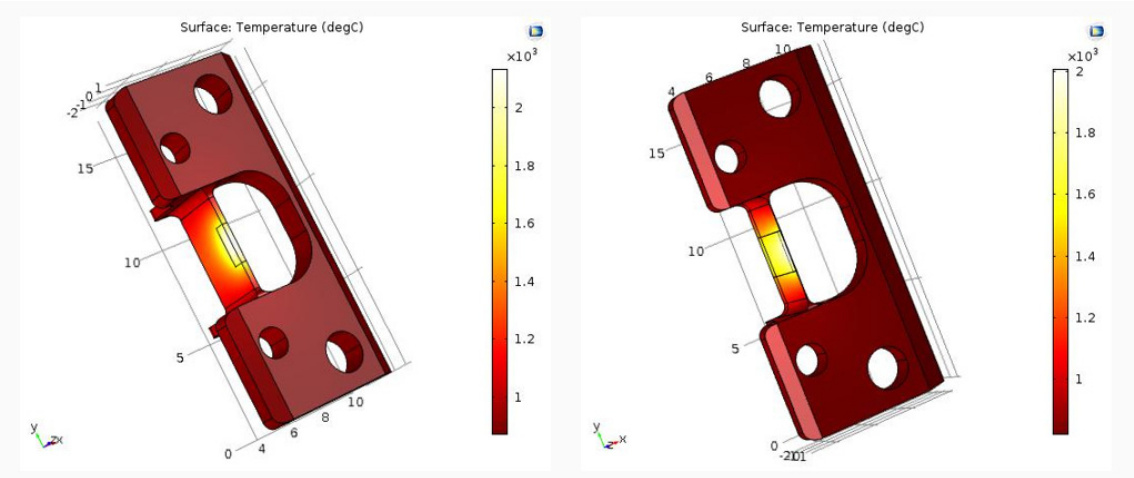

Figure 3. Thermal simulations of collimator used for BG75 Plus target.

The RIG hills will be optimized to ensure that we can achieve > 30 [uA] of beam at a radius of 35.5 [cm]. The current [^{18}F] target is placed at 35 [cm] so movement of the bolts which fix the hills to the upper and lower steel needs to be moved out to ensure that they do not perturb the beam optics at larger radii. Figure 4 illustrates the mechanical displacement analysis performed to ensure that the movement of the bolts does not disturb the magnetic field in the center of the RIG.

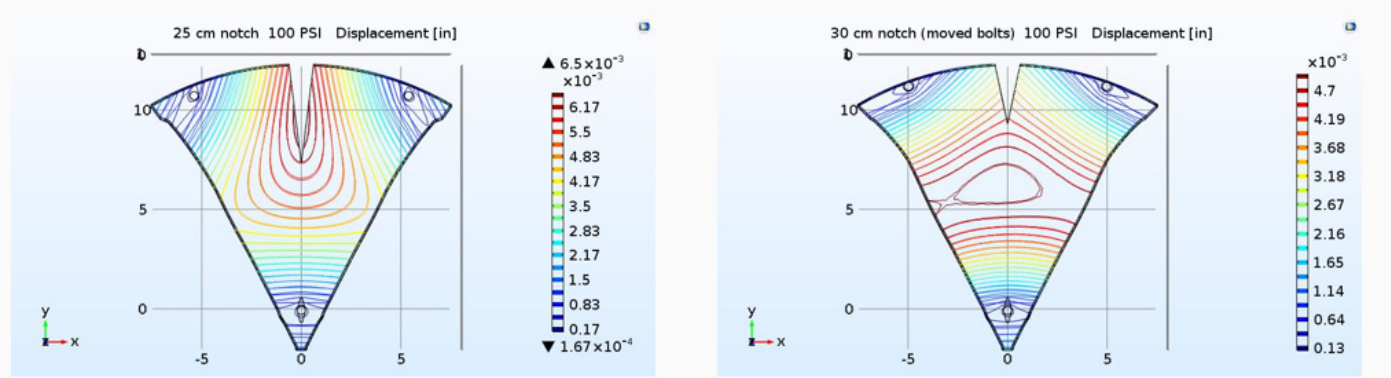

Figure 4. Mechanical displacement analysis of hills to determine the effect of moving the bolt holes out in diameter to achieve a increase in target radius from 35 [cm] to 35.5 [cm].

[^{11}C] Chemistry Card System (CCS) and [^{11}C]Acetate Dose Synthesis Card (DSC

The standard workflow is described below. Figures 7 and 8 illustrate the [^{11}C] CCS and [^{11}C]Acetate DSC for use with the methyl grignard reaction.

Standard Workflow

If the ABT [^{11}C] Automated Synthesis Module is used for clinical injections it will have been stored in 70% Ethanol (EtOH) to prevent growth during periods of non-use. Before beginning synthesis, the system will need to be cleaned and new reagents loaded.

Start of Day (SOD) Clean

- Insert disposable absorbent lint free towel into the DSC slot to retain any cleaning EtOH and water that will be flushed from the transfer lines.
- Run SOD Clean script.
- As the script begins to execute, it will initiate a dialog on the screen requesting the user to pull the aspirating needles (19 g X 3”) to the EtOH, or other storage medium, vial headspace. See Figure 5 for an example of needles in the empty headspace.

Figure 5: Aspirating Needles Pulled to Empty Headspace.

- Mid-way through the clean, the user will be prompted to remove the WFI lines attached to the storage medium needles, attach them to new aspirating needles (19 g X 3”or equivalent), and spike them in a vial containing a sufficient volume of DI water for non-clinical or WFI for clinical use.

Install Reagents

- Prime HCl and NaH_2PO_4 reagent lines for synthesis.
- As the script begins to execute it will initiate a dialog prompting the user to spike the HCL lines to a vial containing a sufficient volume of 2 M HCl and the NaH_2PO_4 line to a vial contain a sufficient volume of 0.5 M NaH_2PO_4 with new aspirating needles (19 g X 3”or equivalent).

Synthesis

- Insert a new [11C] DSC into the CCS such that the top of the DSC is level with the push plate and close the latch.

- From the BG Software, confirm from the plot page (Ctrl+P) that the DSC latch is made (Green). See Figure

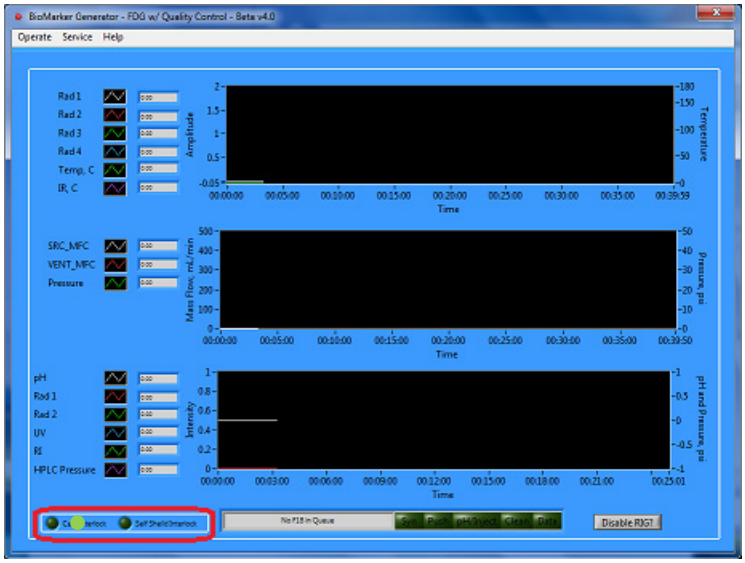

Figure 6: Shield and CCS Interlocks

- Run synthesis script.
- Next, the user will be prompted to begin the cyclotron unload through the molecular sieve [^{11}C]CO_2 trap, DSC, and out to the waste/Trap.
- After the user clicks **OK** the purge gas will be turned off and the user will be prompted to add MeMgBr.
- When the user clicks **OK**, the MeMgBr will be transferred to the reactor vessel.
- At this point, the molecular sieve temperature will be raised to at least 350° [C] and the N_2 carrier gas turned on to begin the release of the [^{11}C]CO_2 to react with the MeMgBr.
- The user will be prompted to stop the unload by turning off the carrier gas.
- The reactor temperature will be raised to 40° [C] for 120 seconds automatically to complete the reaction.
- The temperature will be turned off to allow the reactor to cool down.
- HCl and WFI are added and bubbled for 60 seconds to quench the reaction and add volume for purification.
- Next, the Alumina Purification Column is conditioned with HCl and WFI and flushed with Air and N_2.
- The reactor contents are then pushed across the column trapping the unpurified [^{11}C] acetate.

End of Run (EOR) Clean

- Run EOR clean
- Remove the spent DSC and dispose of it in a site approved manner as it may have residual radioactivity and volatile and corrosive reagents.

End of Day (EOD) Clean

- Insert disposable absorbent lint free towel into the DSC slot to retain any water that will be flushed from the transfer lines.

- Run EOD clean
- As the script begins to execute it will initiate a dialog on the screen requesting the user to pull the WFI aspirating needles to the vial headspace.
- Mid-way through the clean, the user will be prompted to remove the WFI lines attached to the WFI, attach them to new aspirating needles (19 g X 3”or equivalent), and spike them in a vial containing a sufficient volume of EtOH or other growth preventative medium. The HCL and NaH_2PO_4 lines should be moved to the headspace of the waste vial.

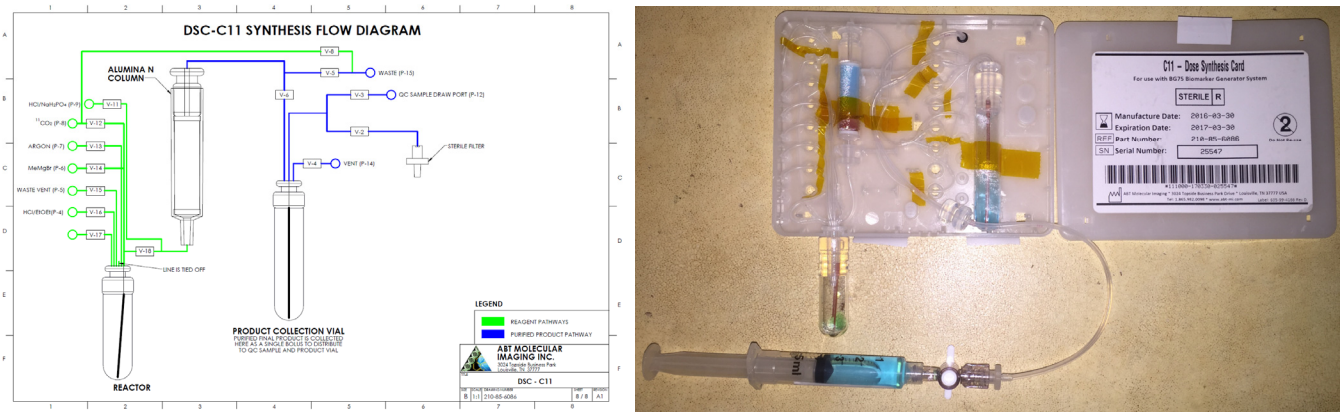

Figure 7. (Left)Schematic of [11C]Acetate DSC using for CGMP production. (Right) Prototype [11C]Acetate DSC used for preclinical testing at the Athinola A. Martinos Center.

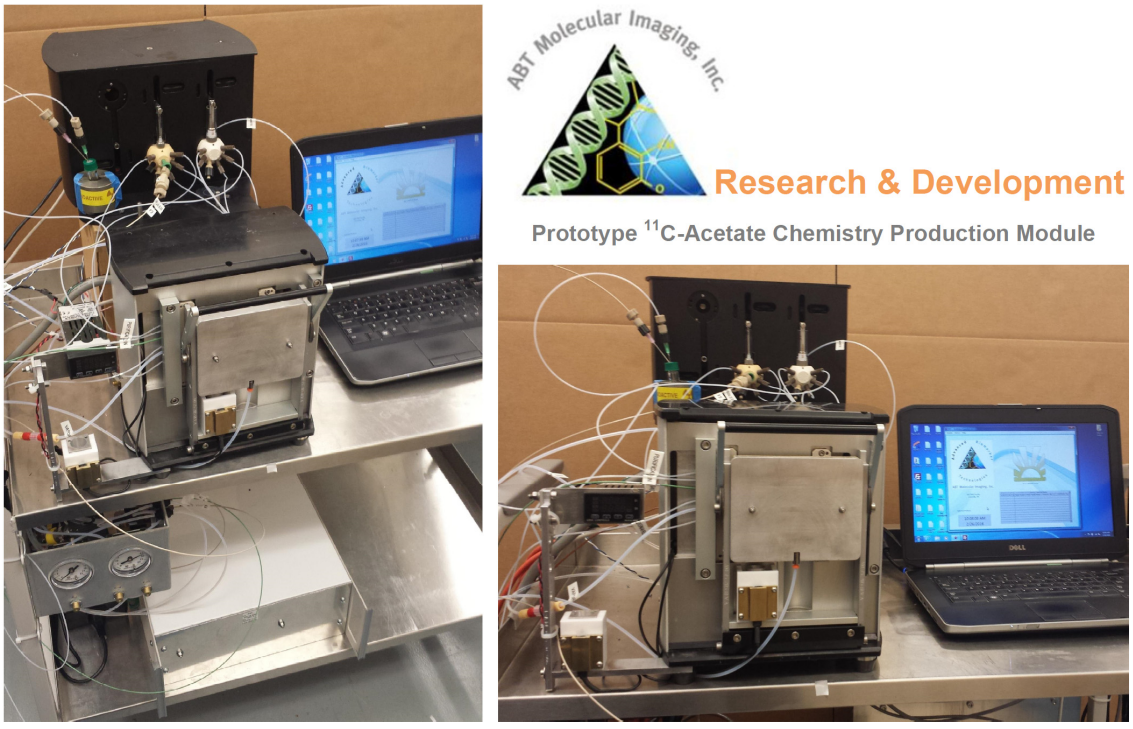

Figure 8. Prototype [11C]Acetate CPM and associate computer used for pinch valve and pump control.

[11C] Quality Control Module (QCM)

Testing has been performed on ABT's integrated and automated QCM to ensure that it will be able to resolve the residual solvents produced from the [11C]Acetate reaction. Based on testing it has been proved that the following parameters will be applicable for [11C]Acetate chemical purity measurements.

300 µl/min flow rate of 100% HPLC water (no additives)
Phenomenex Rezex™ ROA-Organic Acid H+ (8%), LC Column 250 x 4.6 mm*, 78°C

V. CONCLUSIONS:

The BG75 Plus system is under development. The first prototype system is expected by Q2 of 2017 at ABT. Meanwhile, [11C] chemistry will be under testing at MGH for preclinical and clinical injection of [11C]Acetate.

VI. REFERENCES:

1) White Paper - RIG 2.0, Baltimore, MD 2015. http://abt-mi.com/en/resources