Although FDG provides most of the clinical PET imaging today its low specificity limits its use. In molecular imaging technology, highly specific probes for clinical applications are crucial justifying the development of non-FDG radiopharmaceuticals such as: $[^{18}F]$-NaF, for bone metastasis detection; $[^{18}F]$-F-Choline ($[^{18}F$-FCH=methylcholine) for diagnosis/staging of prostate cancer; $[^{18}F]$-FLT, for cell proliferation imaging, and $[^{18}F]$-ML-10 ($\alpha$-methyl 18F-alkyl-dicarboxylic acid), for apoptosis imaging. This work will present automated and optimized processes developed on IBA Synthera® platform for the routine production of $[^{18}F]$-NaF, $[^{18}F]$-FCH, $[^{18}F]$-FLT, $[^{18}F]$-ML-10.

The synthesis of each radiotracer takes place on single-use IFP™ system (integrated fluidic processor) which comprises appropriate pre-defined synthesis hardware and plumbing. $[^{18}F]$-NaF manufacturing is straightforward and employs IFP™ Chromatography. For the $[^{18}F]$-FCH, two synthesizers as well as two interconnected IFP™ (IFP™ Distillation & IFP™ Alkylation) are necessary for the two-step synthesis (fig.1). In synthesis of $[^{18}F]$-FLT and $[^{18}F]$-ML-10 IFP™ Nucleophilic is used. The product obtained is purified in Synthera® HPLC unit. In none of the applications hardware changes are required compatible with a multipurpose platform.

The synthesis of $[^{18}F]$-NaF is obtained by washing trapped $[^{18}F]$ with water followed by elution with saline solution. $[^{18}F]$-FCH is produced in two steps according to published method\(^1\). The first step, performed in IFP™ Distillation, includes the fluorination of dibromomethane (DBM) and purification of fluorinated volatile by distillation through silica cartridges. Next, in the IFP™ Alkylation, fluoromethylation of N,N-dimethylaminoethanol takes place resulting in $[^{18}F]$-FCH which is purified through a cation exchange cartridge. $[^{18}F]$-FLT is produced according to adapted methodology\(^2\).
The synthesis is realized within IFP™ Nucleophilic. $[^{18}\text{F}]-$fluorination of 3-N-Boc-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine (Boc-FLT-Precursor) as well as subsequent acid hydrolysis with diluted HCl are carried out at 100°C. These steps take 10 min. and 5 min., respectively. Crude product is buffered and loaded into reversed-phase HPLC column in Synthera® HPLC for final purification. Ethanol/water is used as mobile phase. Synthesis of $[^{18}\text{F}]-$ML-10 also employs IFP™ Nucleophilic. Both fluorination of the tosylated precursor and consecutive hydrolysis with aqueous HCl were performed at 110°C for 10 min. Buffered reaction mixture was then purified in Synthera® HPLC by reversed-phase HPLC with phosphate buffer/ethanol as mobile phase.

$[^{18}\text{F}]-\text{NaF}$ is obtained in less than 10 minutes with RCY (radiochemical yield) > 90% EOS. Analytical data show it complies with European Pharmacopoeia. Average RCY for $[^{18}\text{F}]-$FCH >20% EOS. The total synthesis time is < 50 minutes. Final product shows high radiochemical purity (99%) and chemical purity (>95 %). $[^{18}\text{F}]-$FLT total synthesis time is 45 minutes (including HPLC purification) with average RCY>20%. Final product presents high radiochemical purity (>95%) and high chemical purity (>95 %). $[^{18}\text{F}]-$ML-10 RCY > 40 % after 60 min of total synthesis time including HPLC purification. Final product presents high radiochemical and chemical purity (> 99%) (fig 2).

![Fig. 2- Typical chromatogram of $[^{18}\text{F}]-$ML10 after HPLC purification](image)

The automated platform has proven to be robust and reliable when it comes to routine production of promising radiopharmaceuticals such as $[^{18}\text{F}]-\text{NaF}$, $[^{18}\text{F}]-\text{FCH}$, $[^{18}\text{F}]-\text{FLT}$ and $[^{18}\text{F}]-$ML-10 for clinical applications. The radiochemical yields obtained are reproducible and final products show high radiochemical and chemical purity. All of the radiopharmaceutical syntheses are carried out within dedicated IFP™ systems (Chromatography, Distillation, Alkylation and Nucleophilic) in one single platform set up with open software for customized applications. The IFP™ is a disposable, preventing cross-contamination, which is line with GMP. The modules are fully interchangeable underpinning the platform multipurpose capability (do-all-in-one platform) and flexibility.

References: