Sequential preparation of two different PET radiotracers employing the Advion NanoTek synthesis system

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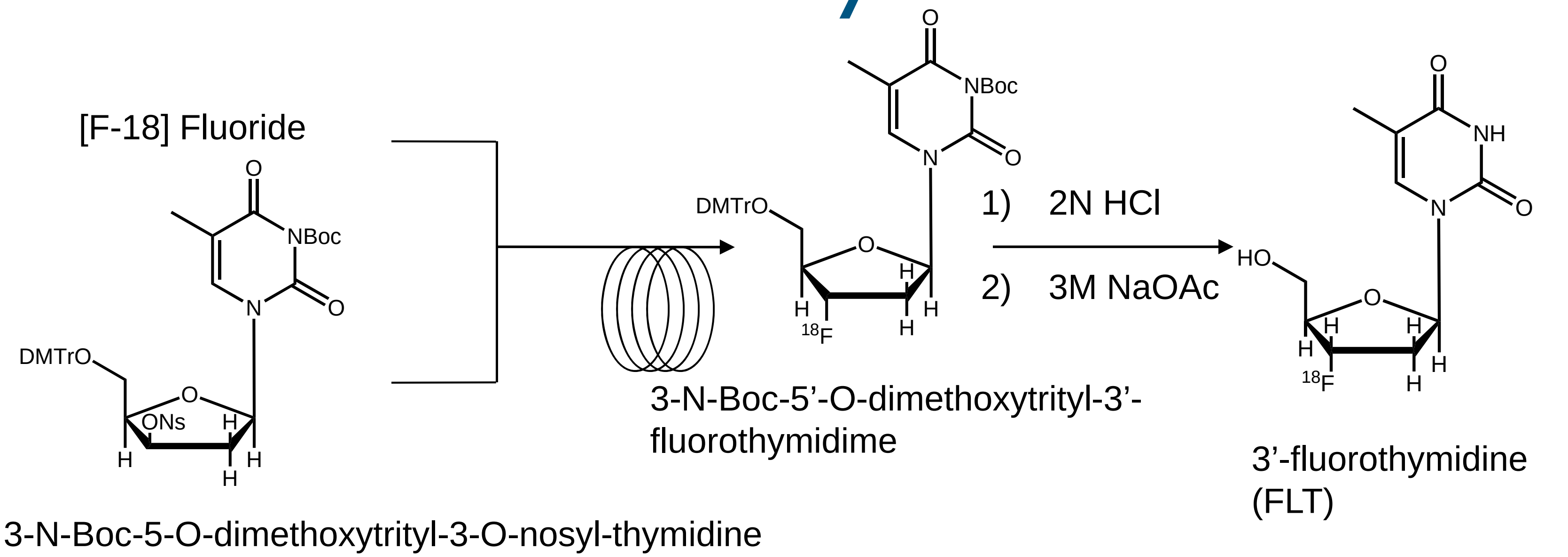
T. Lee Collier- Employee - Advion BioSystems Inc.

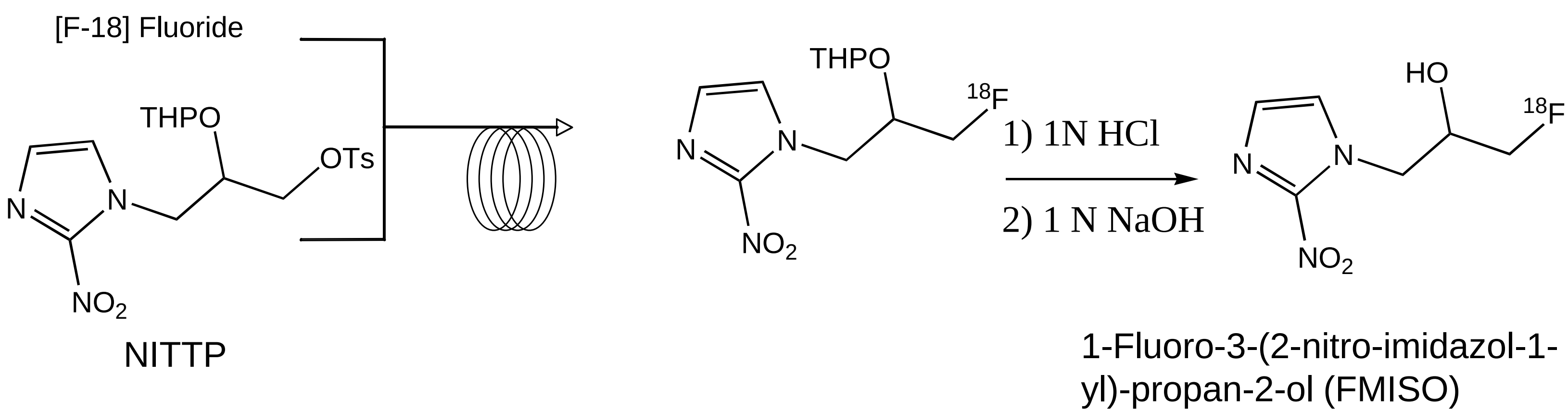
Why do we want to do a Back to Back Synthesis?

To prove that at least two tracers could be made without impacting yield, purity and specific activity

- we chose FLT and FMISO as test tracers
  - these compounds use the most common radiosynthesis methodologies:
    - » Incorporation of Fluoride
    - » Hydrolysis to remove protecting groups
    - » HPLC purification

[F-18]FLT and FMISO Radiosynthesis





System Components

Base Module.
Stores and delivers cold reagents.

Reactor module.
Isotope delivery and reaction.

Concentrator Module
Traps and concentrates F-18.

Distribution valves

Syringe pumps.
48,000 steps

Heated vial

Pressure sensors

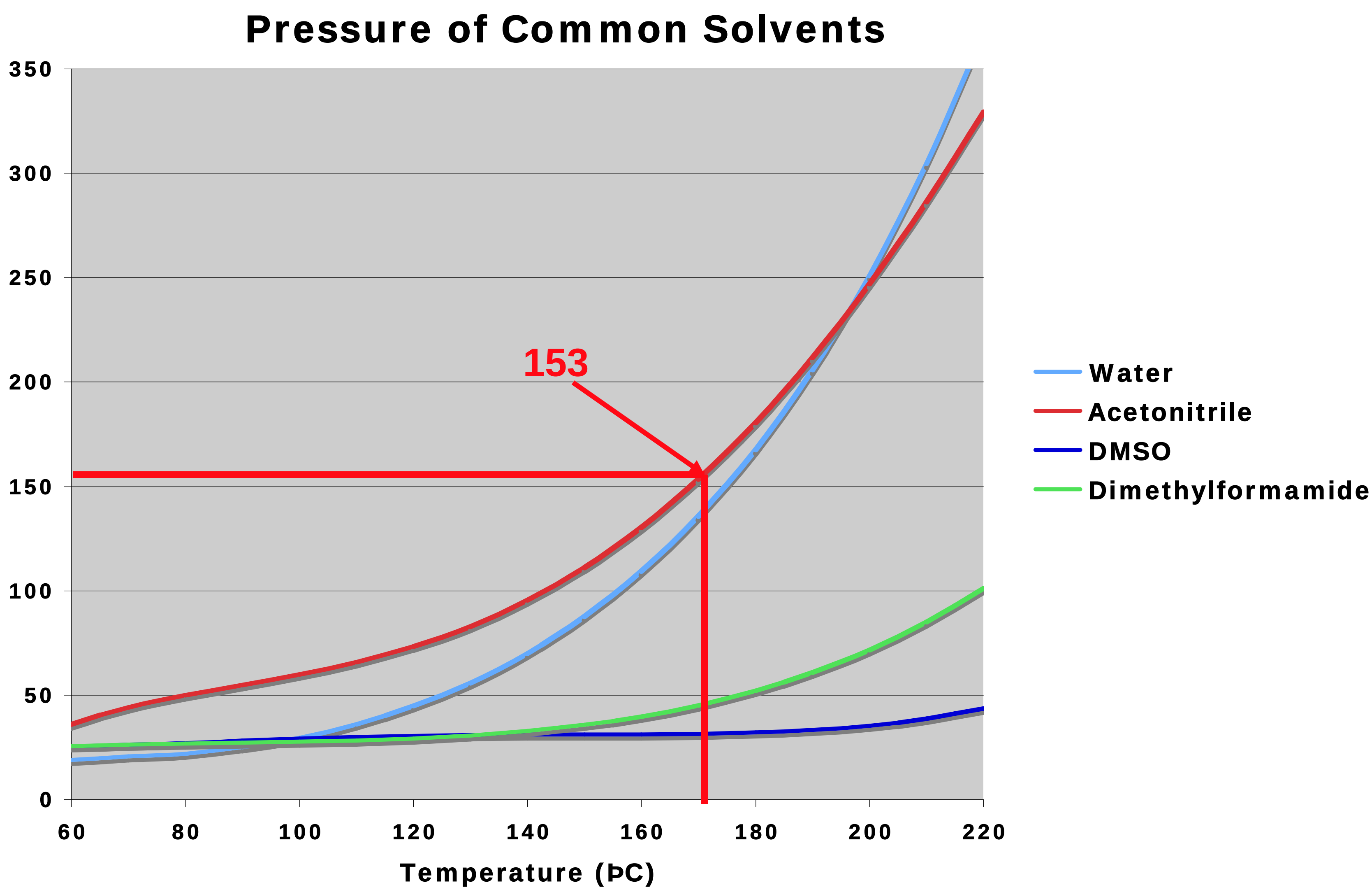
Four independent reactors

Temperature controllers

Dominant effects in Microfluidics

- Faster thermal diffusion
- Laminar flow (Low Reynolds number)
- Surface forces (Capillary phenomenon)
- Liquid evaporation- smaller volume so evaporation has a larger effect
- Gas bubbles - have effects on compressibility

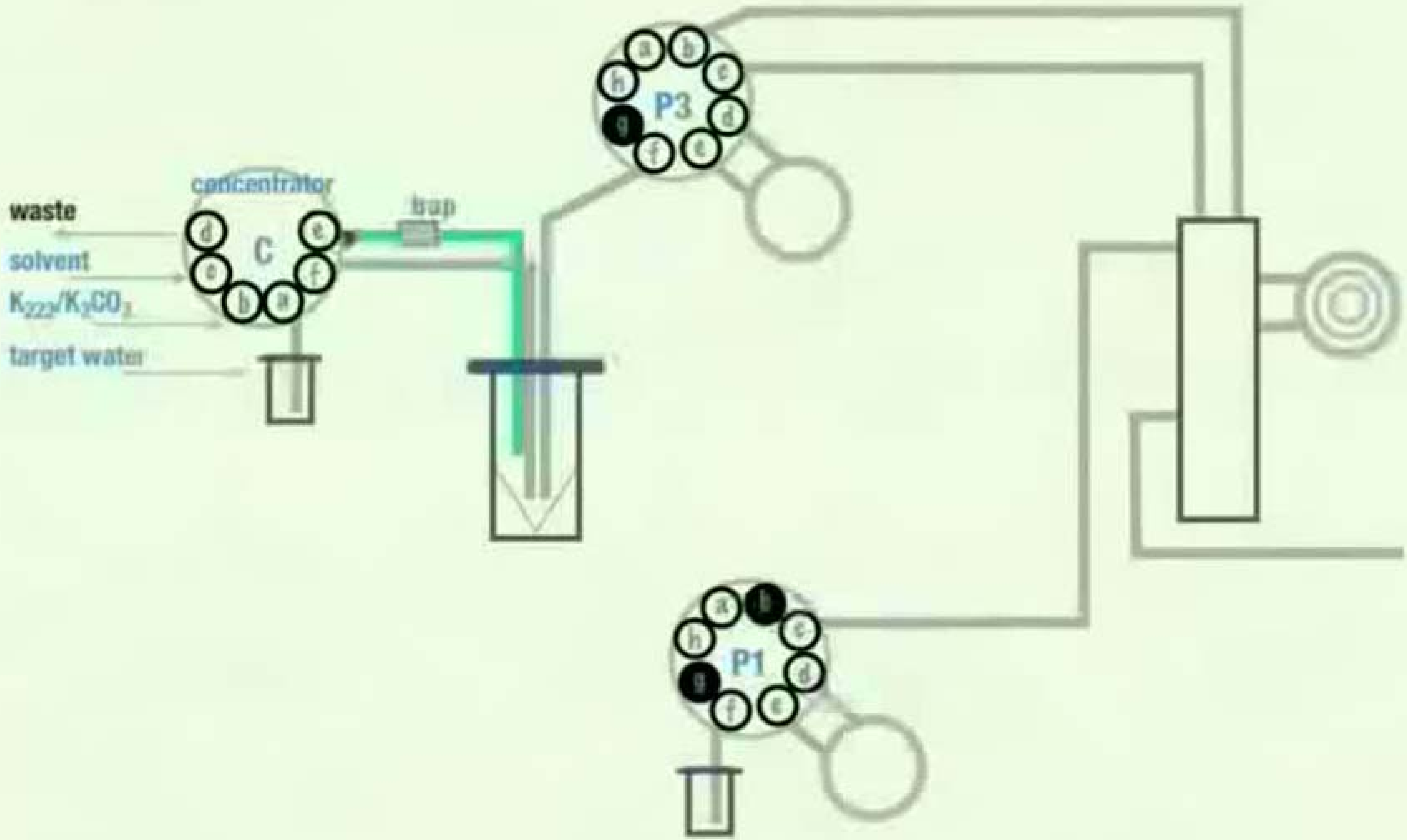
Vapour Pressure



Discovery Mode

- In discovery mode a small aliquot (10-20 µl) from the original solution of of the radioisotope and precursor is mixed in the reactor.
  - This allows the testing of 10-30* different reaction conditions, such as
    - reaction temperature,
    - flow rate,
    - pressure,
    - reagent ratios.
- This can also be done for 2-step reaction.

* The number of reactions are dependent on the volume of solutions loaded to the loops and the size of the bolus used in the reactions



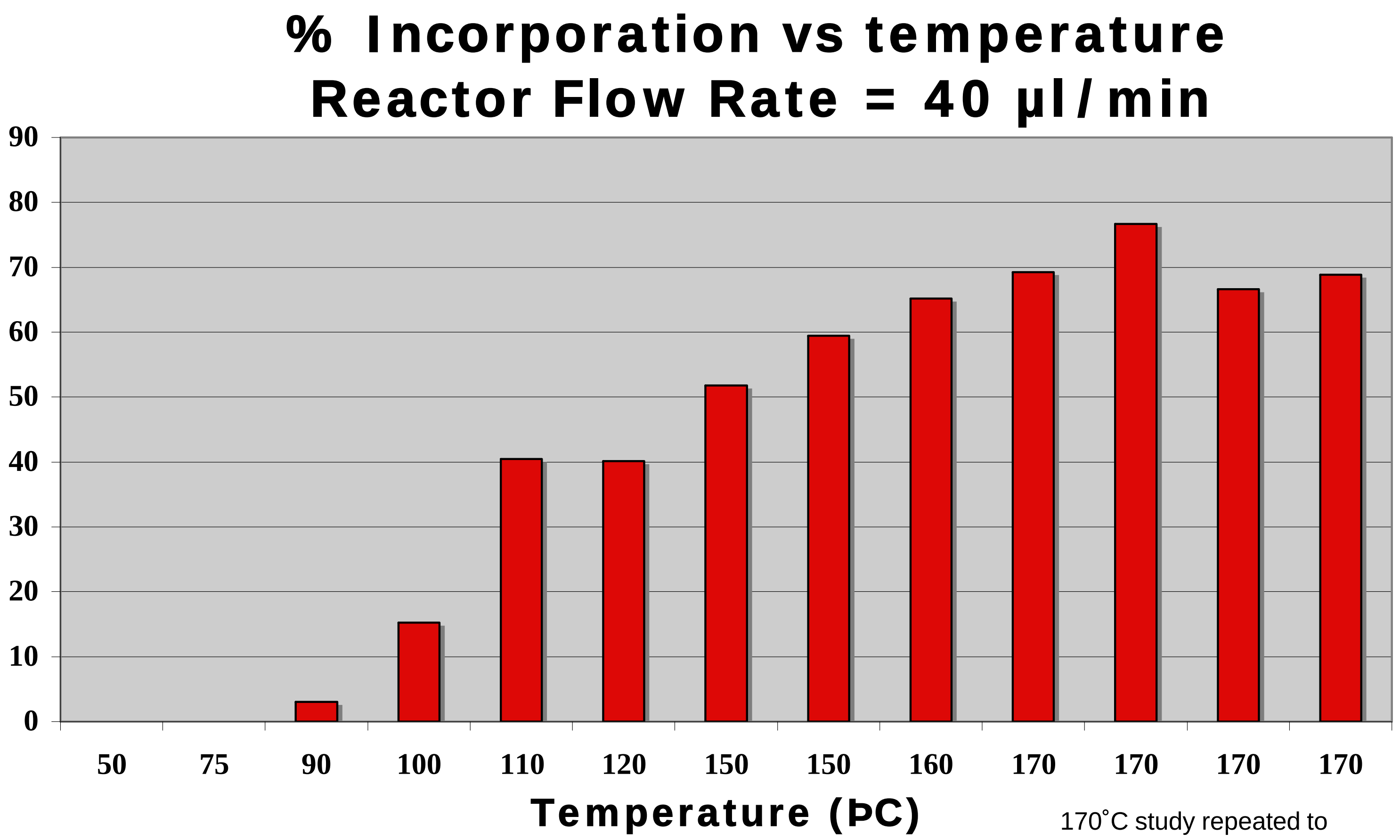
E-mail info@advion.com to request a copy of the animation.

Optimization of [F-18]Incorporation

- **48 Individual Run Experiments**

  Precursor Concentration = 20 mg/ml,

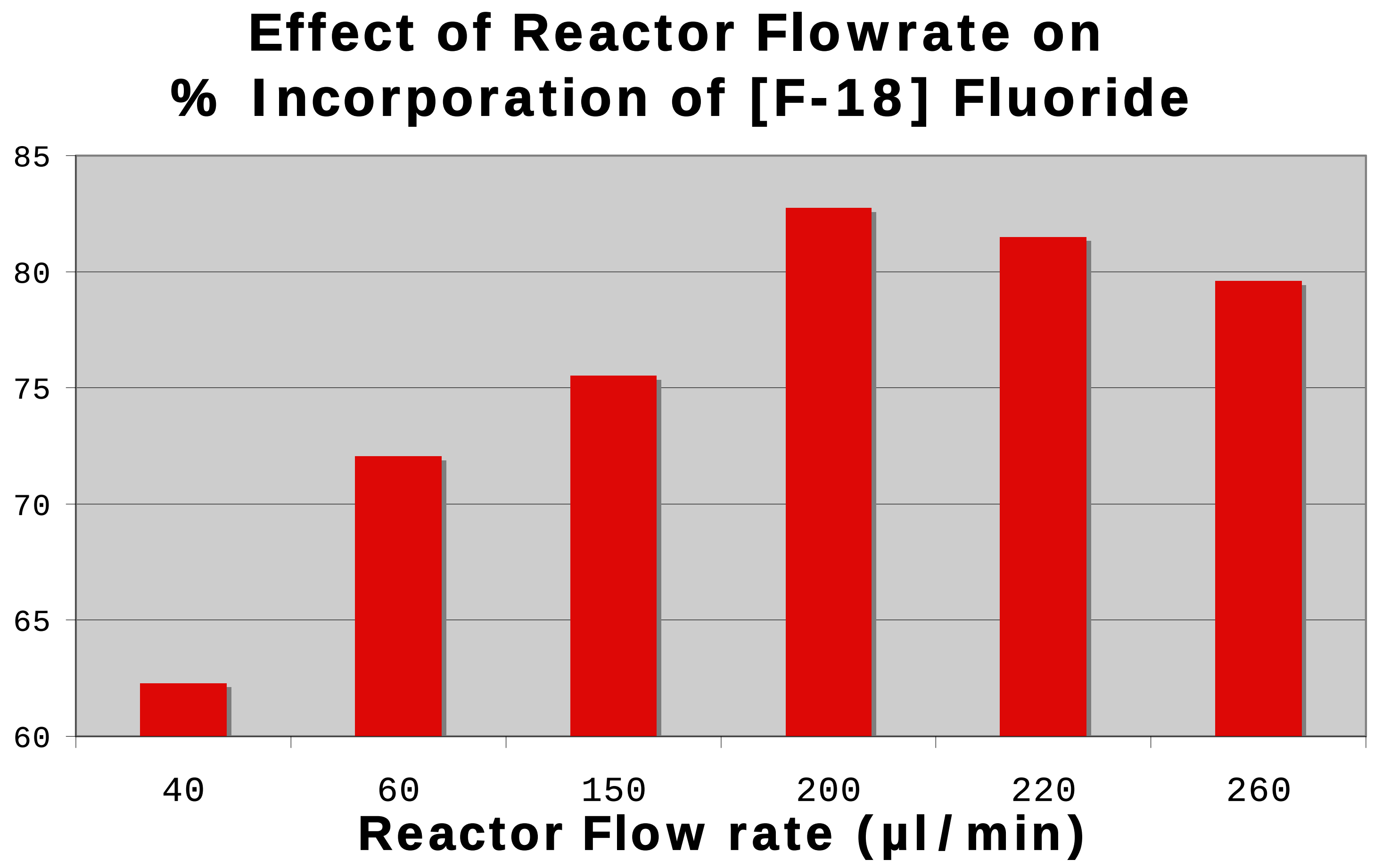
  450 µl / run = 9 mg of precursor / run



170˚C study repeated to determine repeatability

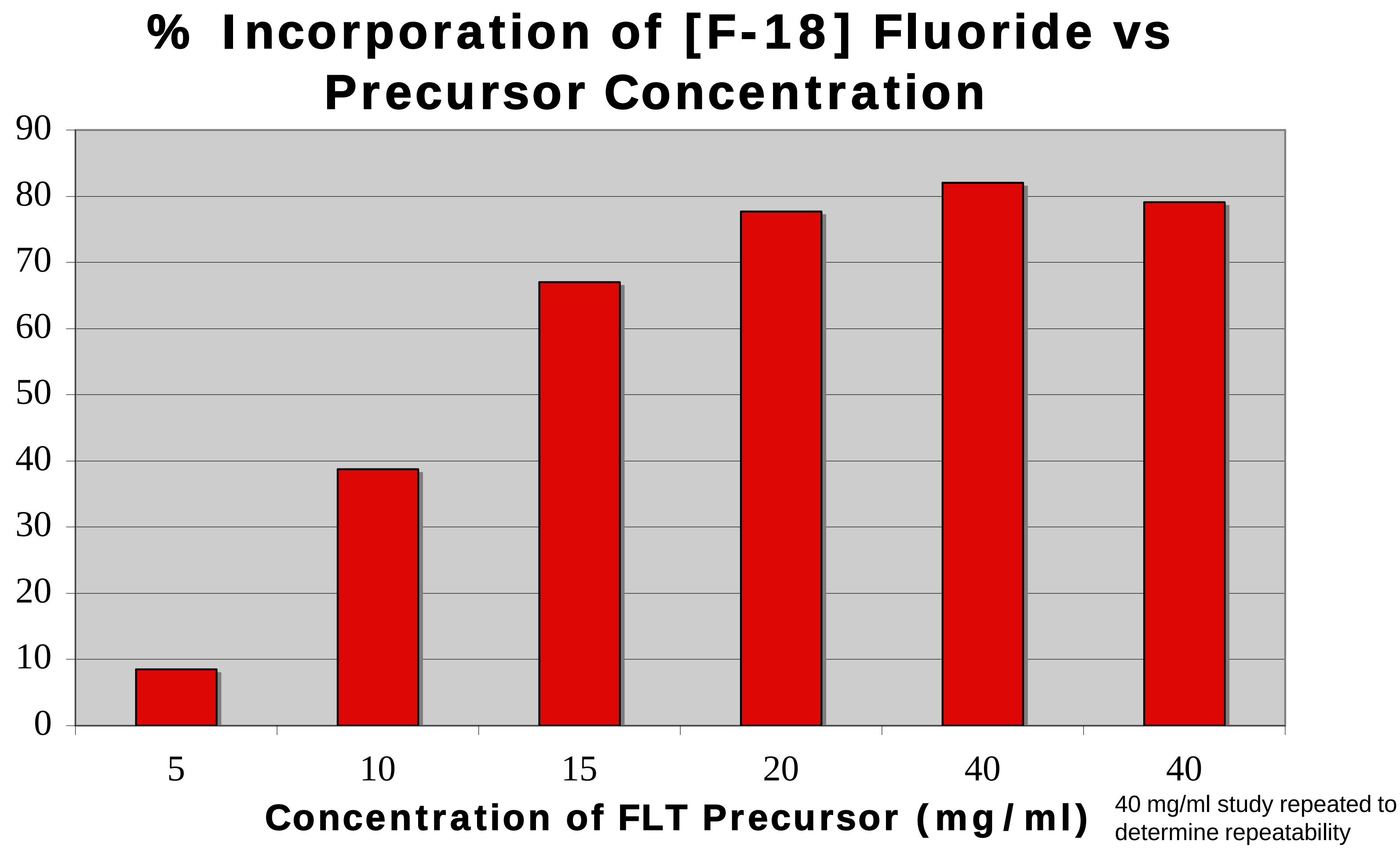
Optimization of [F-18]Incorporation

Precursor Concentration = 20 mg/ml,
450 µl / run = 9 mg of precursor / run



Optimization of [F-18]Incorporation

Precursor Concentration varied from 5 to 40 mg/ml,
Flow rate through reactor = 200 µl/min
Reactor residence time ~5 seconds



Individual Conditions for [F-18]FLT and FMISO

Optimum conditions for FLT

- Reactor Conditions
  - 150-180°C, 150-200 µl/min, 100µm X 2 m
- Reagent Concentrations
  - Precursor 15-40 mg/ml (6-16 mg/run)
  - 2 N HCl, 95°C, 6 minutes
  - 3M NaOAc, 2 minutes, RT

Optimum conditions for FMISO

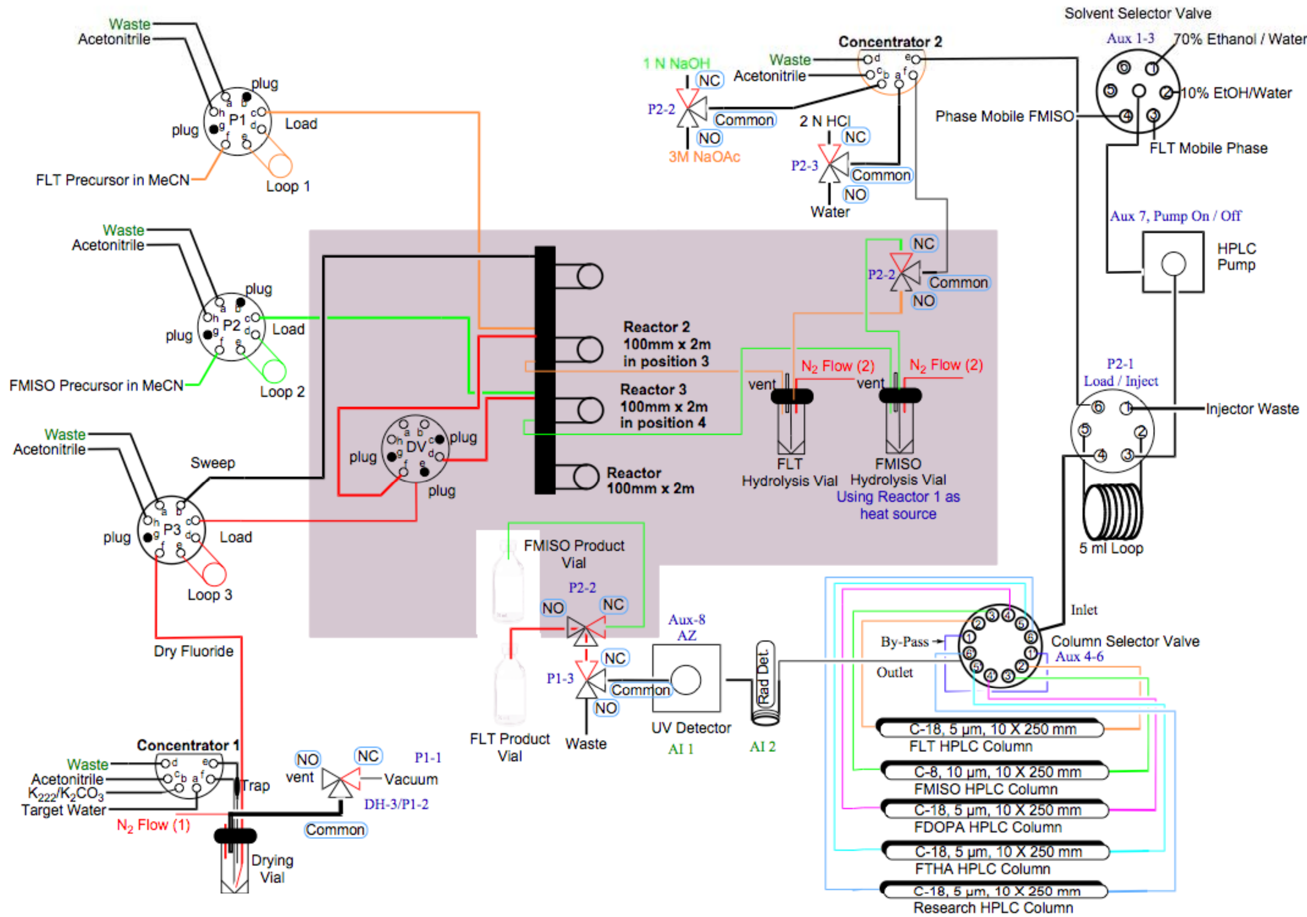
- Reactor Conditions
  - 150-180°C, 150-200 µl/min, 100µm X 2 m
- Reagent Concentrations
  - Precursor 5-10 mg/ml (2-4 mg/ run)
  - 1 N HCl, 100°C, 1 minutes
  - 1 N NaOH, 2 minutes, RT

Requirements for Back to Back Synthesis

Each reaction occurs in an independent flow path

- Fluoride is split in to 2 independent flow paths and mixed with precursor
- Reaction occurs in two different reactors
- Hydrolysis occurs in two separate reaction vials
- HPLC purification occurs on two separate HPLC columns
  - Column selector chooses correct column
  - One column for each compound
- HPLC injector and all associated flow paths are cleaned automatically between tracers
- System can be cleaned fully between runs and low carryover between runs

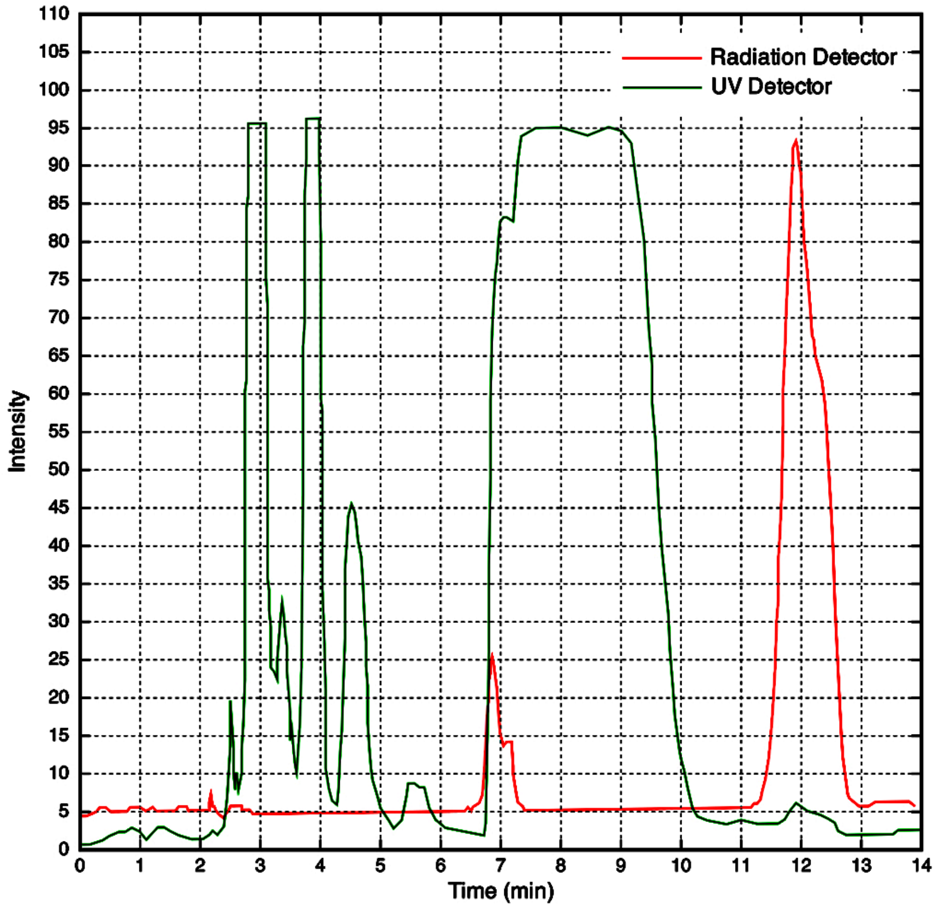
Modifications to Standard NanoTek



Back to Back Radiosynthesis

- To Perform a B2B radiosythesis
  - The user must install prior to starting the Radiosynthesis
    - Kryptofix / carbonate solution and fluoride trap on Concentrator 1
    - 2N Hydrochloric Acid, 3M Sodium Acetate, 1N Sodium Hydroxide, Water
    - FLT precursor on Pump 1
    - FMISO precursor on Pump 2
    - HPLC solvents (70% ethanol / water, 10% ethanol / water, 5% ethanol / water, 8% ethanol / phosphate buffered saline
  - The system will prompt the User for
    - When [F-18]Fluoride is ready and has been transferred to hotcell
    - To inject the crude [F-18]FLT on to the HPLC and to collect the pure [F-18]FLT
    - To inject the crude [F-18]FMISO on to the HPLC and to collect the pure [F-18]FMISO

Purification of [F-18]FLT



As read on the Nanotek system from analogue inputs

Results of B2B Radiosynthesis

B2B Yield when compared with independent reactions (Non-decay corrected yields)

FLT = 20 ± 3% vs 18.9 ± 3% (B2B)

FMISO = 40 ± 5% vs 38 ± 6%(B2B)

Specific Activity >2 Ci/µmol

Runs performed over the range of 50 mCi to 1 Ci

Analysis of the solutions for radioactive and chemical carryover.

The decay corrected radioactive carryover of

0.065% for FLT and 0.031% for FMISO

All other peaks attributable to the chemical carryover resulted in

0.07% for FLT and 0.09% for FMISO

Conclusion

- Two radiotracers were prepared sequentially in
  - Reasonable yield
  - High purity (>99%)
  - No impact on specific activity
  - Tested to a starting activity of 1 Ci
  - System was able to be cleaned with <0.1% carryover
  - Minimum interaction from the end user

Acknowledgements

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