Development of Diaryliodonium Salts as Precursors to $[^{18}\text{F}]$Fluoroarenes

Dr M. A. Carroll
School of Chemistry

CR-UK & EPSRC Cancer Imaging Programme at the Universities of Newcastle and Durham in association with the MRC and Department of Health (England)
Outline

- Medical Imaging at Newcastle
- Fluorine-18 radiochemistry
- Diaryliodonium salts as precursors to $[^{18}\text{F}]$fluoroarenes
- Fluorine-18 oncology/neuroscience tracers
- Summary
Imaging Facilities

- Clinical MRI (Philips 3T)
- Pre-clinical MRI (Varian 7T)
- Clinical PET-CT (Siemens Biograph 40)
- Pre-clinical PET (Philips), CT (Bioscan)
Why restricted to $[^{18}\text{F}]$FDG?

Challenges

- No systematic studies to optimise radiolabelling process (>5 Ci)
- Few combination studies (different isotopes and techniques)
- Low material yield
- Low radiochemical yield + RCY(DC)
- Low specific activity (isotopic dilution)
- Label is incorporated where it is easy to introduce
  - not necessarily where it is needed!
- Short half lives
  - conventional synthetic routes/procedures not appropriate
- Metabolism
- Automation/translation to clinical setting
**[¹⁸F]Fluorine Chemistry**

Starting material is [¹⁸F]fluoride anion in [¹⁸O]H₂O

- **Aromatic fluorine**
  - enhanced metabolic stability
  - restrictions on the aromatic ring
  - restrictions on the substituents

- **Aliphatic fluorine**
  - limited metabolic stability
  - restrictions on the position
  - restrictions on other substituents

- **Fluorine ‘tags’**
  - can be aromatic or aliphatic
  - requires suitable linking group \( X = \text{NH}_2, \text{OH}, \text{SH}, \text{COOH} \)

Radiopharmaceutical Production

- Radiochemical yield - RCY
- Decay corrected radiochemical yield – RCY(DC)
- Specific activity - radioactivity per mole of compound

1. Transfer of $^{18}$F from cyclotron to radiosynthesis unit
2. Trapping and drying of $[^{18}\text{F}]$fluoride
3. Reaction of $[^{18}\text{F}]$fluoride to make imaging agent (may be multi-step)
4. Isolation/purification of imaging agent
5. Formulation
6. Transfer to scanner ready for injection (passed QC)
Technology: Selection Criteria

- $[^{18}F]$fluoride is the starting material of choice
- $[^{18}F]$fluoroarene preferred
- No restriction on the:
  - electronic nature of the target (hetero)aromatic ring
  - steric constraints of the target (hetero)aromatic ring
  - substitution pattern of the target (hetero)aromatic ring
- Compatible with multiple and sensitive functionality
- Single-step generic process
  - technology fit with existing automation
Iodonium Route to $[^{18}F]$Fluoroarenes

- Diaryliodonium salts may be prepared:–
  - by direct aromatic substitution
  - from aryltrialkylstannanes
  - from arylboronic acids

$[^{18}F]$Fluoride: high specific activity
- electron-deficient and electron-rich (hetero)aromatic rings
- no restriction on substitution pattern
- control of ring selectivity on fluorination

For some examples see:-
Synthesis of Ethyl-3-[\textsuperscript{18}F]fluorobenzoate

All compounds in the initial studies, using our routine screening conditions, provided the target 3-\textsuperscript{18}Ffluoro derivative in practical yields.

[\textsuperscript{18}F]Fluorobenzaldehyde, [\textsuperscript{18}F]FBA

Addition of Water in the Fluorination of 1

\[
\text{RCY} \% = \begin{cases} 
5\% \text{ Water} & \uparrow \\
10\% \text{ Water} & \uparrow \\
20\% \text{ Water} & \uparrow \\
\text{No Water} & \uparrow 
\end{cases}
\]

Heteroaromatics: 3-[\textsuperscript{18}F]Fluoropyridine

Carroll et al., US12/647,169
Rapid Purification: Fluorous SPE

\[
\text{CF}_3\text{COO}^- + \begin{array}{c}
\text{Ph} \text{I} \\
\text{COOEt} \end{array} \rightarrow \begin{array}{c}
\text{Ph}^+ \\
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{O} \text{C}_6\text{F}_{13} \text{Et} \end{array} \\
\text{COOEt} \end{array} + \begin{array}{c}
\text{I} \\
\text{Ph} \text{O} \text{C}_6\text{F}_{13} \text{Et} \end{array}
\]

Reproducibility: Radical Scavengers

- The addition of a radical scavenger e.g. TEMPO improved reproducibility

Steric Effect

Carroll et al., *J. Labelled Compd. Radiopharm.*, 2008, 51, 259
4-[^18F]SFB: Typical Approach

- 4-[^18F]SFB: Most commonly used prosthetic group
- Multi-step, multi-pot synthesis
- Difficult to automate

Iodonium Route - challenge

- Reduce the number of reaction steps
- Selective reaction of [^18F]fluoride in the presence of the active ester
- Generic approach to all regioisomers

4-[^18F]SFB: Iodonium Approach

4-[^18F]SFB: The first single-step synthesis
- Selective for both \(^{19}\text{F}\) and \(^{18}\text{F}\)
- Other non-participating aromatic rings may be used
- Suitable for automation

Optimisation of process (yield/automation) and application as a prosthetic group is currently underway

Radiochemistry Laboratory

**FIRST PET radiochemistry facility in the North East**

- Located:
  School of Chemistry

- Research & pre-clinical production of fluorine-18 radiopharmaceuticals

- 2 PET research hotcells

- Refurbishment Q1 2009
- Operational (\(^{18}\text{F}\)) Q4 2009

- Future proof design
  - additional hotcells
  - PET & SPECT isotopes
Synthetic Radiochemistry

- **Batch production**
  - Eckert & Zeigler Modular Lab
  - Multi-step, flexible system

- **Microwave**
  - Resonance Instruments
ABT: Biomarker Generator ‘mini-cyclotron’

- 7.5 MeV Positive Ion Cyclotron
- 3 Internal targets
- Production Rate of 1.0 mCi/min $[^{18}\text{F}]$fluoride
- 1.16 T Magnet
- 2-5 µA Beam current
- 250 µL Target Volume
[\textsuperscript{18}F]Fluorine Targets in Oncology

- Glucose metabolism
  - [\textsuperscript{18}F]FDG

- Hypoxia
  - [\textsuperscript{18}F]FMISO

- Cellular proliferation
  - [\textsuperscript{18}F]FLT

- PARP
  - [\textsuperscript{18}F]AG140699

- Choline transport
  - [\textsuperscript{18}F]FEC

- Amino acid transporters
  - [\textsuperscript{18}F]FET
[\textsuperscript{18}F]Fluorine Targets in Neuroscience

- \(5\text{HT}_{1A}\)
  - \([\textsuperscript{18}F]\text{MPPF}\)

- \(D_2\)
  - \([\textsuperscript{18}F]\text{Fallypride}\)

- \(\beta\)-amyloid
  - \([\textsuperscript{18}F]\text{AV45}\)

- \(5\text{HT}_2\)
  - \([\textsuperscript{18}F]\text{Altanserin}\)

- dopamine metabolism
  - \([\textsuperscript{18}F]\text{FDOPA}\)

- dopamine transporters
  - \([\textsuperscript{18}F]\text{FMT}\)

- \([\textsuperscript{18}F]\text{FECNT}\)
- 'peripheral' benzodiazepine
  - [18F]DAA1106

- benzodiazepine
  - [18F]Flumazenil

- noradrenaline transport
  - [18F]FMeNER-d2

- α7 nicotinic
  - [18F]NS10743

- α4β2 nicotinic
  - [18F]nifene

- mGluR5
  - [18F]MTEB

- neurokinin type-1 receptors
  - [18F]SP-A-RQ
Biomacromolecules: peptides, antibodies, oligonucleotides

- ‘amine/alcohol’ selective
  - ![Chemical structure](image)

- ‘thiol’ selective
  - ![Chemical structure](image)

- ‘carboxylate’ selective
  - ![Chemical structure](image)

- other
  - ![Chemical structure](image)
PET Radiochemistry - Summary

- ALL of the major methods for incorporation of fluorine-18 have been achieved ($S_N2$, $^{19}F/^{18}F$, $S_NAr$, iodonium)
- $[^{18}F]$Fluorination has been achieved, both batch and microfluidic systems
- Microwave and conventional heating have been employed
- Pre-clinical production of a range of imaging agents:
- New methodology and targets in progress
- Precursor production:
  - automation, robust/reproducible, high purity, QC
  - GMP grade material

Next steps

- ABT Biomarker Generator, carbon-11 and other radioisotopes
- Clinical production – MHRA Specials Licence
- Expand the range of pre-clinical imaging agents – single kit design
Newcastle - Chemistry
L. M. Kamara  P. D. Hancock
J. Woodcraft  P. K. D. Dawson
S.-L. Tang    Dr S. Hobson
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Dr G. Smith   C. Reed
Dr R. Yan     M. Charlton
Dr L. Dixon   C. McCardle
E. Fisher     S. Bhatt

Imperial College
Dr. D. A. Widdowson
Dr. E. Wilson
Dr H. S. Rzepa
Dr S. Martin-Santamaria

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Dr L. Brichard

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‘I+PET’ Technology

- Improved preparation of known targets

  ![Diagram of the current route](image)

  35-45 min $\rightarrow$ 1 min

- Access to ‘impossible’ targets

  ![Diagram of 3-[18F]pyridine](image)

  63%

Unique understanding/skills in the preparation and purification of ‘I+PET’ reagents
4-[^{18}F]SFB: Iodonium Approach
Newcastle - Fine Chemical Production

'on-demand' synthesis of organics

- Multi-step synthesis of both precursors and imaging agents
  - reduce synthetic steps (pre- and post-labelling)
  - enhanced purity requirements *cf.* APIs
  - uses many metal catalysed steps
    (key: selectivity, rate, mild conditions)
    (reagents with low reactivity e.g. $[^{11}C]CH_4$, $[^{11}C]CO$, $[^{11}C]CO_2$)
  - rapid optimisation required (automated process)
  - flow and batch processes (micro and meso)
  - scale range (mgs – 100gs – kgs)
  - translate rapidly to GMP
  - specific Newcastle technology **NOT** restricted to fluorination
PET: Applications/ Potential

- Almost any biological process may be studied
- Range of half-lives and elements available
- Low dose – typically ng or pg required (limits toxicity)
- Label species of interest
- Diagnostic – response to treatment
- Biological data
  - Combination with other techniques – MRI, CT
- Real-time monitoring
  - improved data handling/processing
- *in vivo* data
- whole body: off-target activity, non-specific binding
- Early in the drug development process
Fluorine-18 Automation

- **Batch (Eckert & Zeigler Modular Lab)**
  - $[^{18}\text{F}]\text{FEC}$

- **Microwave**
  - $[^{18}\text{F}]\text{MPPF}$

34.67% radiochemical incorporation
Synthetic Radiochemistry

- **Microfluidic** production
  - Advion NanoTek LF
  - Multi-step, flexible system
Fluorine-18 Automation

- Microfluidic (Advion NanoTek)
  - Variation of multiple reaction parameters
  - Rapid optimisation of protocols (>30 runs per batch of $[^{18}F]$fluoride)
  - Robust performance
  - Introduction of Et$_4$N.HCO$_3$ as a new phase transfer reagent
  - **ALL** reaction types now achieved
Radioanalytical Systems
- radioHPLC (Agilent 1200)
- radioGC (Agilent 6890)
- radioTLC (Bioscan AR2000)

Summary
- Very flexible radiosynthetic & analytical facility
- Batch and microfluidic production
- Range of $[^{18}\text{F}]$fluoride chemistries possible
- Small molecule and biomacromolecule targets
Integrated Chemistry and QC

- Lead Shield
- Chemistry Card
- Syringe Pump
- Radiation Detector Probe
- Gas Manifold
- NI RIO Chassis
- Power Supply (24 vdc)
- Reagent Metering Kit
- HPLC Column
- UV Detector
- RI Detector
- Isocratic Pump
- Degasser
- Waste container mounted on side