$^{68}$Ga microfluidics

Dezső Szikra$^{1,2}$, Gábor Máté$^1$, Gábor Nagy$^2$

1. Institute of Nuclear Medicine, University of Debrecen, Debrecen, Hungary
2. Scanomed Ltd., Debrecen, Hungary

COST meeting
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University of Debrecen, Institute of Nuclear Medicine

- GE PETtrace (16.5 MeV cyclotron)
- GMP production
- more than 500 FDG batch/year (8-10,000 doses)
- 50 $^{11}$C-methionine batch/year
- $^{11}$C-choline just received marketing authorization
- http://www.nuklmed.deoec.hu/
Scanomed Ltd. Debrecen

- 10 cameras (2 PET/CT)
- 8200 SPECT scans/year
- 4400 PET/CT scans/year
- 30 isotope diagnostic tests
- Iodine and Zevalin therapy
- clinical trials
- www.scanomed.hu
PET microfluidics

- reaction in channels with diameter < 1 mm
- large reaction surface
- high thermal conduction
- easy control and optimization of the reactions
- high reproducibility
- high throughput
- well established for $^{11}$C and $^{18}$F chemistry
Microfluidic radiolabeling of biomolecules with PET radiometals


5-8uM $^{68}$Ga$^{3+}$, 100-160uM NOTA-RGD, 37°C
Why should we replace the pipette?

- Better reproducibility (heating, mixing)
- Low precursor consumption (μl volumes)
- Automatic optimization (pH, concentration, temperature, reaction time)
- On-line HPLC analysis
- On-line purification
Home-built microfluidic system

- Syringe pump
- Injector valve
- HPLC pump
- Reactor
- Online HPLC
- Autosampler with precursors
- Capturing valve

- $^{68}\text{Ga}^{3+}$
- 10,5m x 0,15 mm PEEK capillary
- 10 ul Ga + 10 ul HEPES buffered chelator
- Reaction conditions: 95°C, 5 min.
- 20 ul reaction mixture injected onto column
Home-built HPLC autosampler

- 15 sample
- Internal/external needle wash
- 2 wash cycles
- Cross contamination <0.3% (UV det.)
- 10ul injection volume
- Partial loop filling
- RSD = 0.29%
Control: Arduino Mega 2560 R3
Code written in Arduino

```cpp
// Code written in Arduino

readingStep = digitalRead(stepPin);
readingHome = digitalRead(homePin);
readingExtEmpty = digitalRead(extEmptyPin);
readingExtFill = digitalRead(extFillPin);

// ****************************STEP
if (readingStep != lastStepState) {
    lastStepTime = millis();
}
if ((millis() - lastStepTime) > debounceDelay) {
    stepState = readingStep;
    if (stepState == HIGH) {
        motorSpeed = 300;
        stepper.setMaxSpeed(motorSpeed);
        stepper.setSpeed(motorSpeed);
        stepper.move(780);
    }
}
```
Gallium injector

- 10 ul loop
- injection with loop overfilling
- RSD = 0.6%
Circulated air thermostat

- 10,5m x 0,15mm PEEK capillary
- Fan
- Heating coil
- Temperature stability: ±0,1°C
HPLC separation of $^{68}$GaNOTA and $^{68}$Ga$^{3+}$

Adsorbosphere XL SCX 5μ 250x4,6mm
A: water
B: 0,2M tartaric acid
C: 5% NaCl
0min: 65%A, 30%B, 5%C
5min: 65%A, 30%B, 5%C
7min: 0%A, 30%B, 70%C
13min: 0%A, 30%B, 70%C
Optimization experiments with NOTA

Radiochemical purity (%)

Ligand concentration (μM)

pH

95.0 - 100.0
0.0 - 95.0

Radiochemical purity (%)

Ligand concentration (μM)

pH

95.0 - 100.0
0.0 - 95.0
Manual vs. microfluidic
# Production experiments

<table>
<thead>
<tr>
<th>Material</th>
<th>Ligand concentration (μM)</th>
<th>Flow rate (mL/min)</th>
<th>Reaction time (min)</th>
<th>Measured activity/Injected activity (%)</th>
<th>Radiochemical purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOTA</td>
<td>10</td>
<td>0.066</td>
<td>5</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>NOTA</td>
<td>10</td>
<td>0.132</td>
<td>2.5</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td>NOTA</td>
<td>10</td>
<td>0.264</td>
<td>1.25</td>
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<td>99</td>
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<tr>
<td>NOPO</td>
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<td>0.066</td>
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<td>99</td>
</tr>
<tr>
<td>NODAGA-(RGD)$_2$</td>
<td>10</td>
<td>0.066</td>
<td>5</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>NOPO-RGD</td>
<td>1</td>
<td>0.066</td>
<td>5</td>
<td>99</td>
<td>97</td>
</tr>
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</table>
Gallium adsorption

68Ga-retention (%)

pH dependence of the zeta potential


HEPES!

NOTA labeling in acetate buffer

30μM NOTA, pH 3
Gallium adsorption from acetate buffer

![Graph showing Ga-retention vs pH](image)

Graph with pH on the x-axis and 68Ga-retention (%) on the y-axis, showing data points and error bars.
Why should we carry on?

Aims of gallium chemistry

• Development of gallium generator with no germanium breakthrough
• „Perfect chelator” selectively coordinates $^{68}$Ga from unpurified eluate
• Final purification can be avoided by using small precursor/buffer amounts → microfluidics

• But: eluate has to be concentrated into microliters
• Can be a useful tool for preclinical experiments