

Streamlined Production of [^{18}F]OP-801 and Radiation Dosimetry to Enable Clinical Translation for Imaging Neuroinflammation

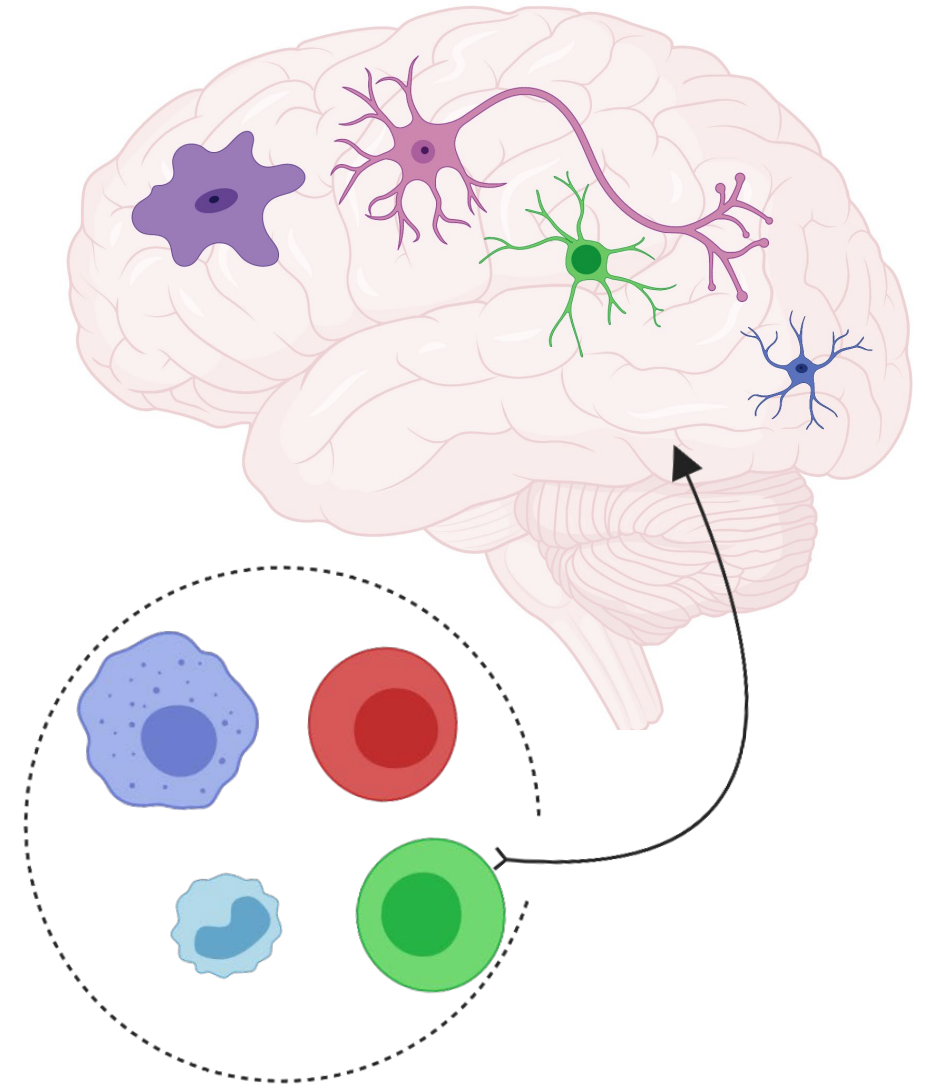
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The Potential Clinical Impact of Neuroinflammation Imaging

The innate immune component of neuroinflammation plays a critical role in the pathogenesis and progression of many neurological diseases

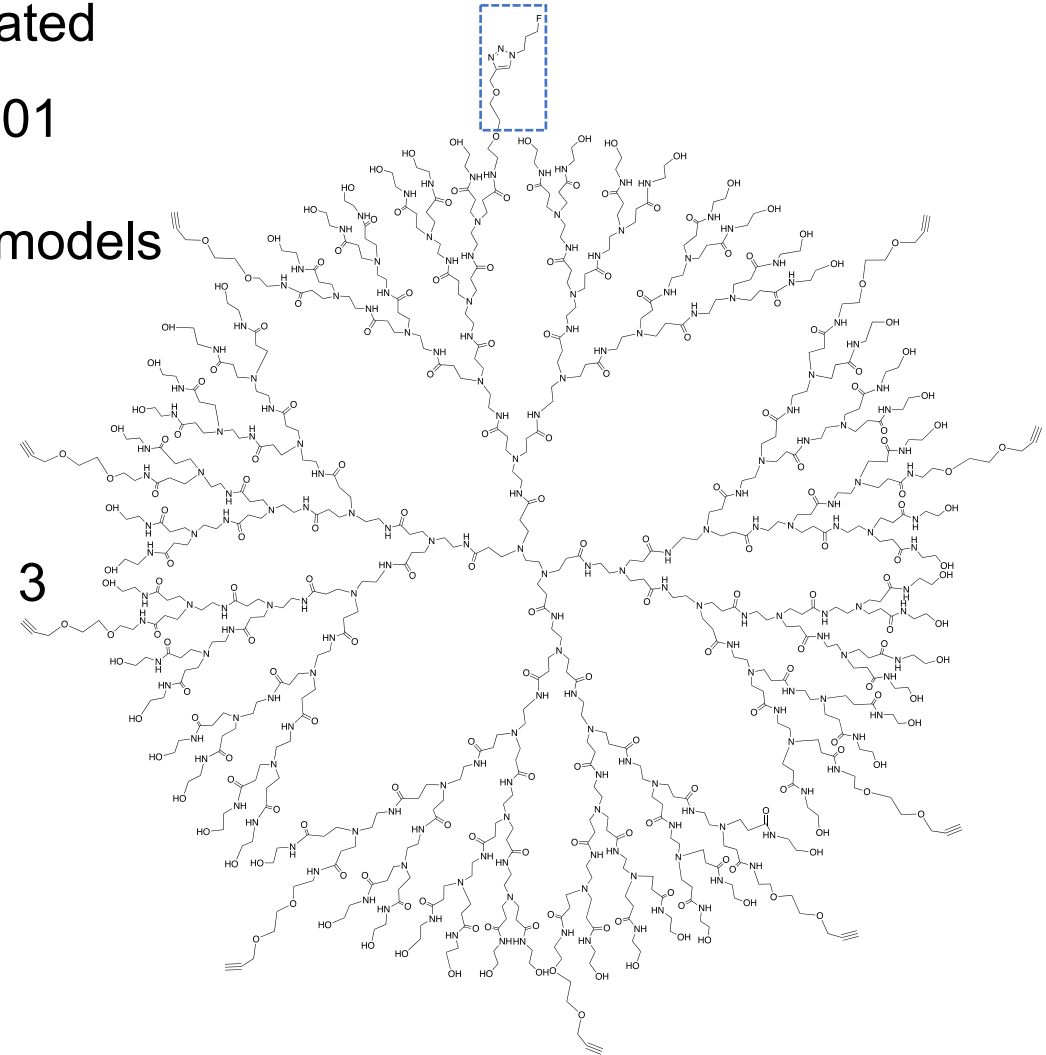
Unmet need: there are no clinically available methods for specifically tracking microglia and their function *in vivo*

Impact: PET approaches for neuroinflammation imaging have high potential to enable longitudinal assessment of immune function over the course of disease progression and treatment



Development of Dendrimer Based PET Tracer [^{18}F]OP-801

- **PAMAM hydroxyl dendrimer** taken up by activated microglia and macrophages (>95%) called OP-801
- Cy5 fluorescent analogue tested in > 30 animal models
- Metabolically stable in humans, complete renal excretion
- [^{18}F]OP-801 developed at Stanford, evaluated in 3 murine models of neuroinflammation



Development of Dendrimer Based PET Tracer [^{18}F]OP-801

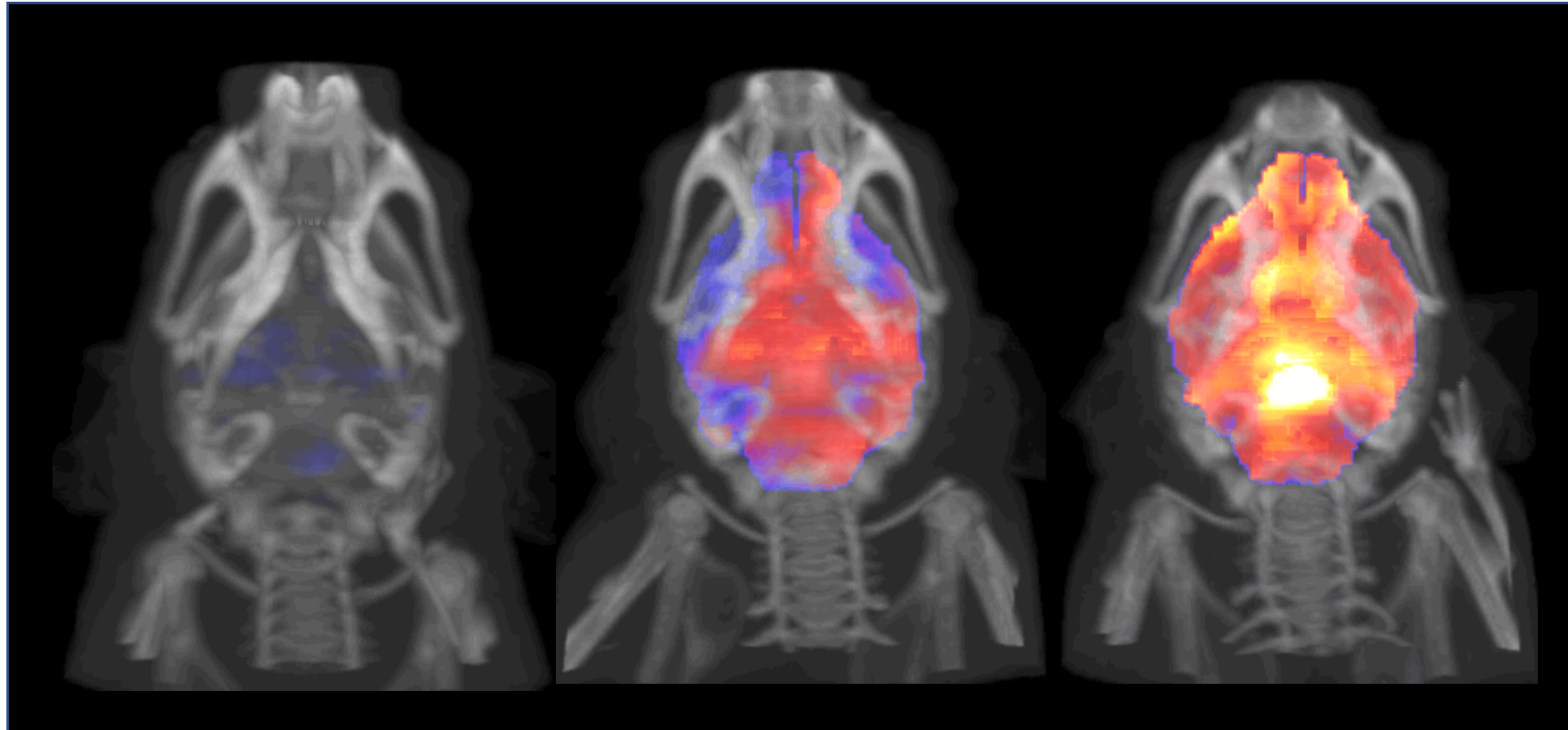


Mackenzie Carlson

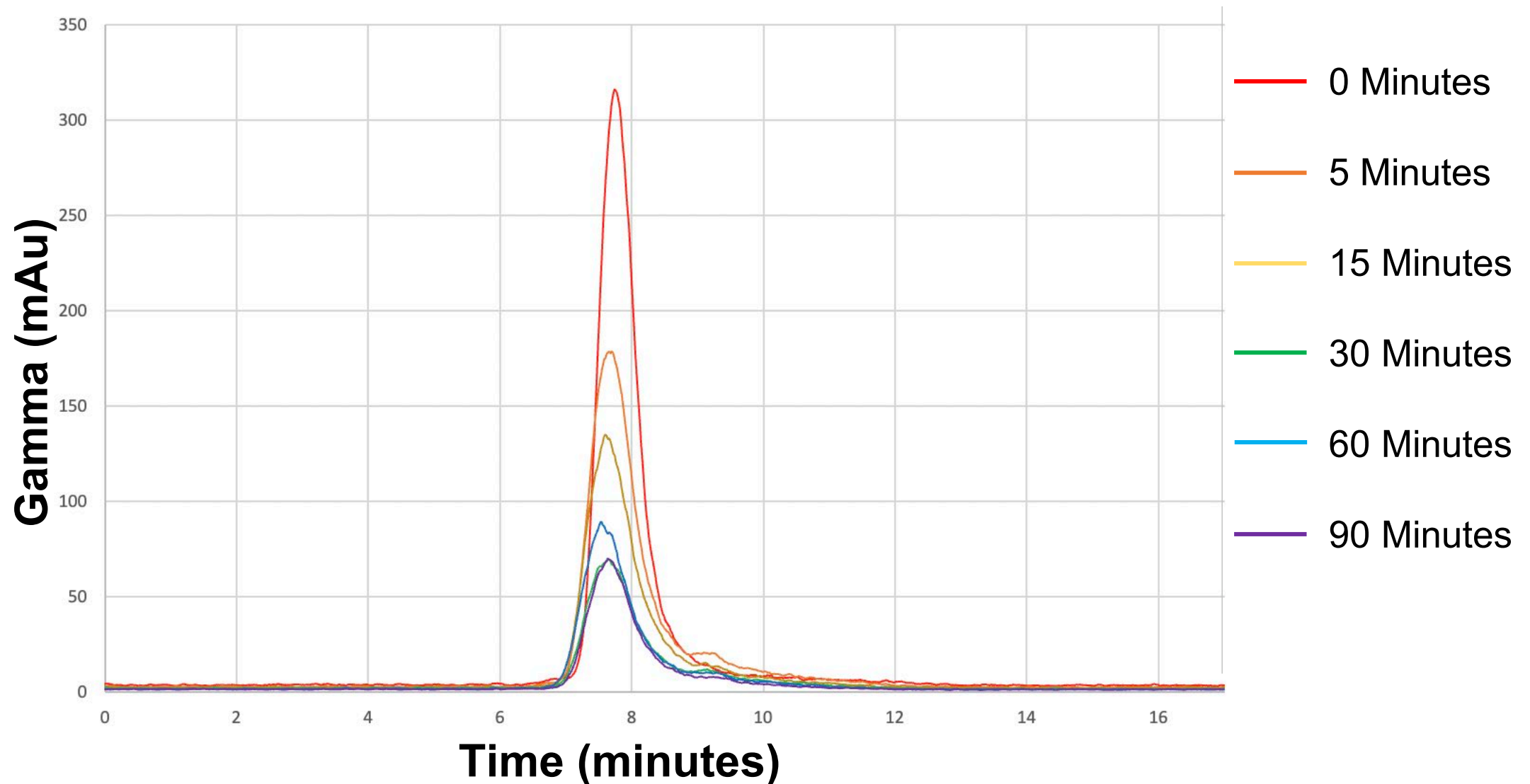
Saline Control

LPS (Moderate Sepsis)

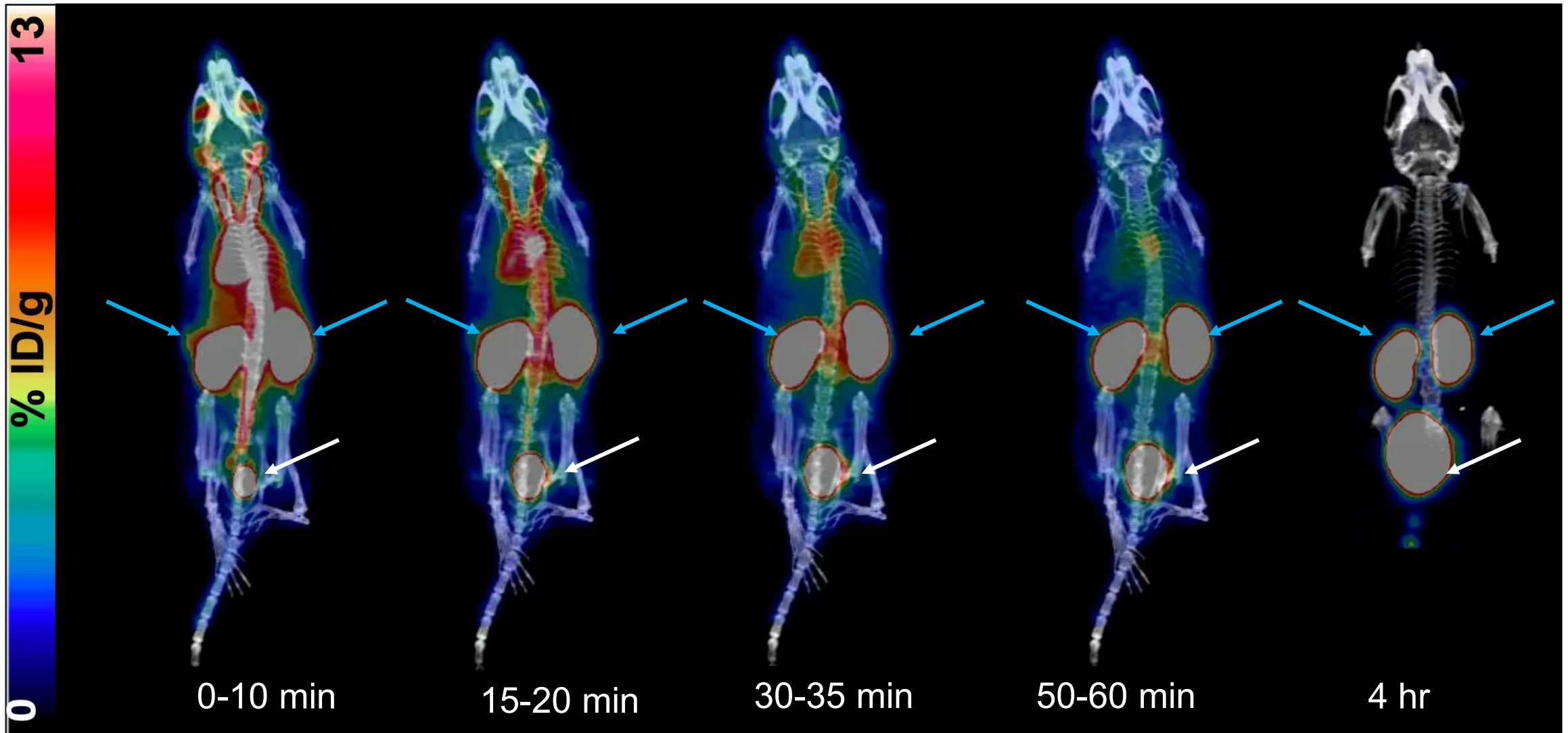
LPS (Severe Sepsis)



In vitro stability is conducive to *in vivo* imaging



Imaged-based studies in mice predict human dosimetry



Imaged-based studies in mice predict human dosimetry

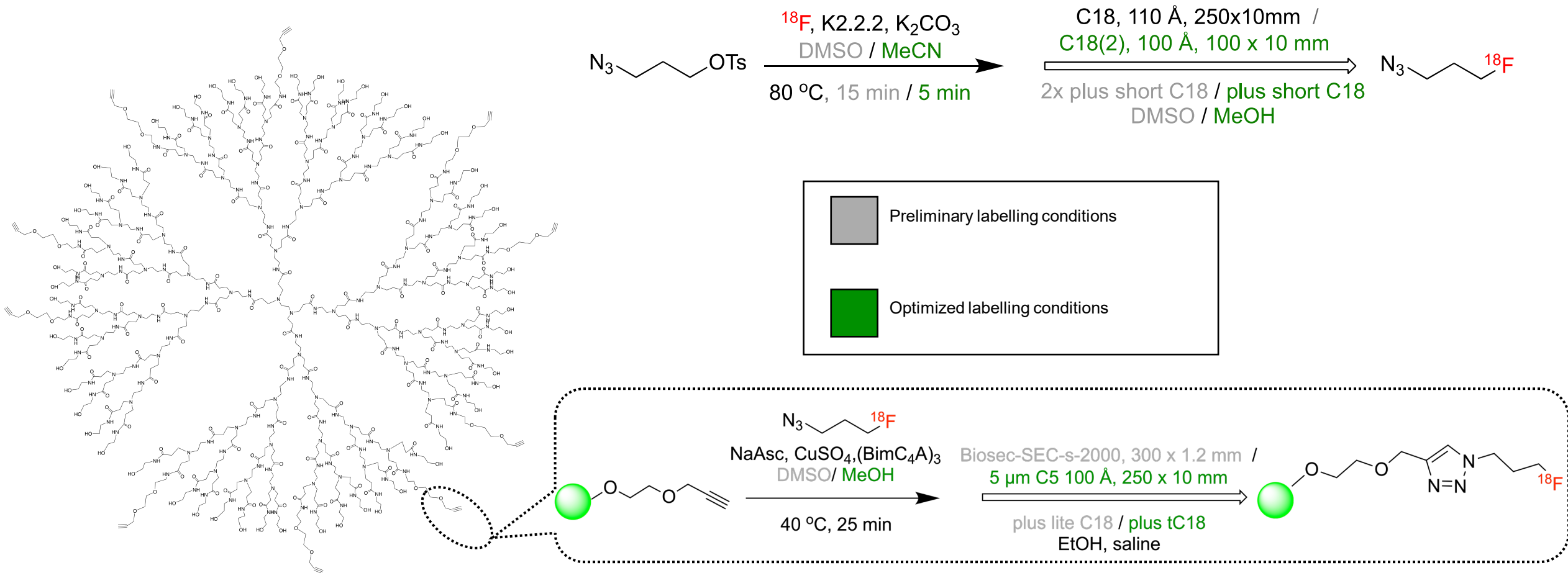
Organ	Human Total Dose Equivalent			
	Female		Male	
	rem/mCi	rem/MBq	rem/mCi	rem/MBq
Adrenals	6.22E-03	1.68E-04	7.62E-03	2.06E-04
Brain	1.68E-03	4.55E-05	2.89E-03	7.82E-05
Breasts	1.03E-03	2.78E-05	1.38E-03	3.73E-05
Gallbladder Wall	4.22E-03	1.14E-04	5.62E-03	1.52E-04
LLI Wall	6.29E-03	1.70E-04	3.05E-03	8.23E-05
Small Intestine	4.22E-03	1.14E-04	3.42E-03	9.24E-05
Stomach Wall	2.57E-03	6.94E-05	3.59E-03	9.70E-05
ULI Wall	3.64E-03	9.84E-05	3.37E-03	9.12E-05
Heart Wall	6.14E-03	1.66E-04	6.51E-03	1.76E-04
Kidneys	1.17E-01	3.15E-03	1.67E-01	4.52E-03
Liver	9.07E-03	2.45E-04	9.92E-03	2.68E-04
Lungs	9.77E-03	2.64E-04	1.03E-02	2.79E-04
Muscle	4.26E-03	1.15E-04	5.07E-03	1.37E-04

Organ	Human Total Dose Equivalent			
	Female		Male	
	rem/mCi	rem/MBq	rem/mCi	rem/MBq
Ovaries	6.36E-03	1.72E-04		
Pancreas	4.40E-03	1.19E-04	5.99E-03	1.62E-04
Red Marrow	2.78E-03	7.51E-05	3.10E-03	8.38E-05
Osteogenic Cells	1.91E-03	5.17E-05	2.42E-03	6.55E-05
Skin	1.24E-03	3.35E-05	1.48E-03	4.01E-05
Spleen	4.88E-03	1.32E-04	6.40E-03	1.73E-04
Thymus	1.63E-03	4.41E-05	2.42E-03	6.55E-05
Thyroid	8.07E-04	2.18E-05	1.79E-03	4.85E-05
Urinary Bladder Wall	1.98E-01	5.34E-03	3.33E-02	9.00E-04
Uterus	1.15E-02	3.10E-04	4.33E-03	1.17E-04
Total Body	3.89E-03	1.05E-04	4.48E-03	1.21E-04
Testes			2.05E-03	5.54E-05
Effective Dose	1.51E-02	4.08E-04	9.69E-03	2.62E-04

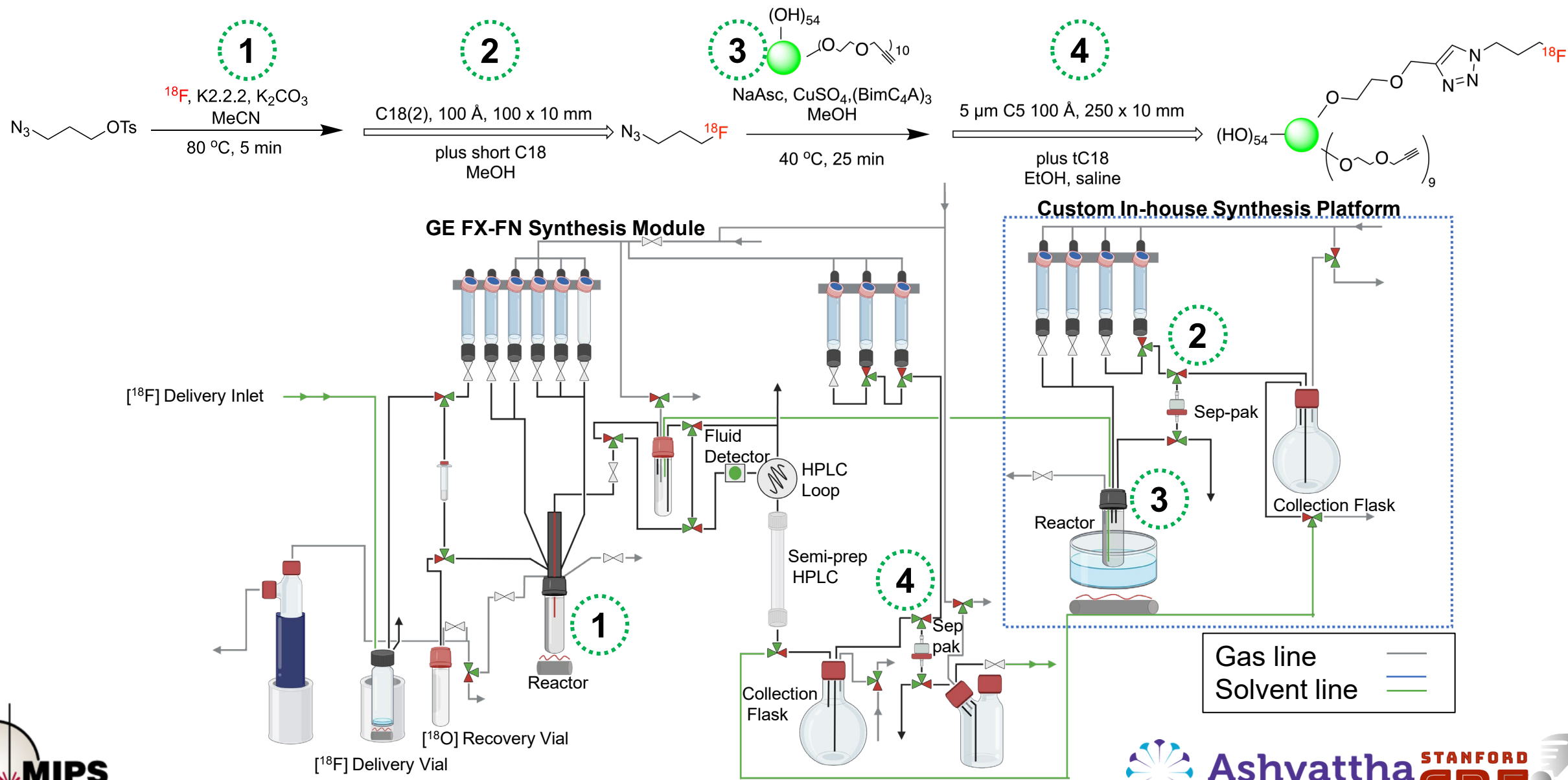
Maximum dose per scan is 1106.3 MBq (females), 1587 MBq (males)

New Synthesis is Optimized for Low Mass Dose Imaging

Toxicology study established mass dose limit: 0.100 mg



Optimized Synthesis can be Automated for Clinical Production



Automated Synthesis is Validated for Clinical Production

Property	Method of Analysis	Release Criteria	Time of Test
pH	pH indicator strips	pH 4.5-8.0	Pre-release
(Radio)-Chemical Purity	Analytical HPLC	≥90% purity	Pre-release
Specific Activity at TOI	Analytical HPLC	<100 µg OP-801 and derivatives in whole batch	Pre-release
Organic Residues	Gas chromatography	≤410 ppm acetonitrile, ≤3000 ppm methanol, ≤ 10% ethanol	Pre-release
Filter Integrity	Bubble-point test	≥45 PSI	Pre-release
Bacterial Endotoxins	LAL bacterial endotoxin test	<175 EU/batch	Pre-release
Identification	Analytical HPLC Co-injection	Rt [¹⁸ F]OP-801 – Rt [¹⁹ F]OP-801 ref std < 1.0 min	Pre-release
Visual Inspection	Visual check of vial integrity	Clear, colorless, free of particulate	Pre-release
Radionuclidic Identity	Dose Calibrator, MCA	t _{1/2} 105-115 mins, photon peak= 0.511 MeV	Pre-release
Kryptofix (K2.2.2)	TLC	No Iodine spot in [¹⁸ F]OP-801 lane	Pre-release
Sterility	USP Sterility Test	negative	Post-release

Key Takeaways and Future Directions

- Murine dosimetry and *in vitro* stability studies of [^{18}F]OP-801 are conducive to clinical imaging
- [^{18}F]OP-801 can be synthesized in yield and specific activity amenable to human imaging
- Automated radiosynthesis of [^{18}F]OP-801 has been validated and approved for clinical translation
- First-in-human clinical [^{18}F]OP-801 imaging studies in healthy humans and ALS patients are scheduled for Q4 2022

Acknowledgements

Thank you for your attention!

James Lab

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New Synthesis is Optimized for Low Mass Dose Imaging

Yield and Specific Activity for Validated Clinical [^{18}F]OP-801 Synthesis

	Validation 1	Validation 2	Validation 3	Avg (Stdev)
Starting ^{18}F (MBq)	74629	77811	93240	81893(9954)
Final Activity (MBq)	1924.7	2311.02	4240.2	2825.32(1240.45)
Specific Activity (GBq/mg)	32.93	24.79	54.76	37.49(15.49)
Activity Yield	2.87%	3.3%	5.06%	3.74%(1.16%)
Radiochemical Yield	5.12%	6.17%	9.39%	6.89%(2.23%)
Synthesis time (Minutes)	92	99	98	96(3)

New Synthesis is Optimized for Low Mass Dose Imaging

Average Mass Dose and Molar Activity by Synthesis Procedure

	Activity/Mouse (MBQ)	Molar Activity (GBQ/Mmol)	Mass/Mouse (µg)
High Mass Preclinical (N=3)	4.78	28.50	4.30
Low Mass Optimized (N=4)	4.10	154.678	0.42
Low Mass Validation (N=3)	3.49	569.96	0.10