Automated Arterial Blood Sampling in Rhesus Monkey PET Imaging Studies

LT Gantert[1]; K Riffel[1]; C Salinas[1]; T Baldini[3]; M Holahan[1]; H Haley[1]; M Purcell[1]; S Wang[2]; D Posavec[1]; A Joshi[1]; DE González Trotter[1]

Department of [1]Translational Biomarkers, [2]Biometrics Research, Merck Research Laboratories, Merck & Co., Inc., Kenilworth, NJ, USA, [3]Instech Laboratories, Plymouth Meeting, PA, USA

Liza T. Gantert
BS in Animal Science – University of Rhode Island
Merck Translational Biomarkers – Nuclear Imaging Physiology Group

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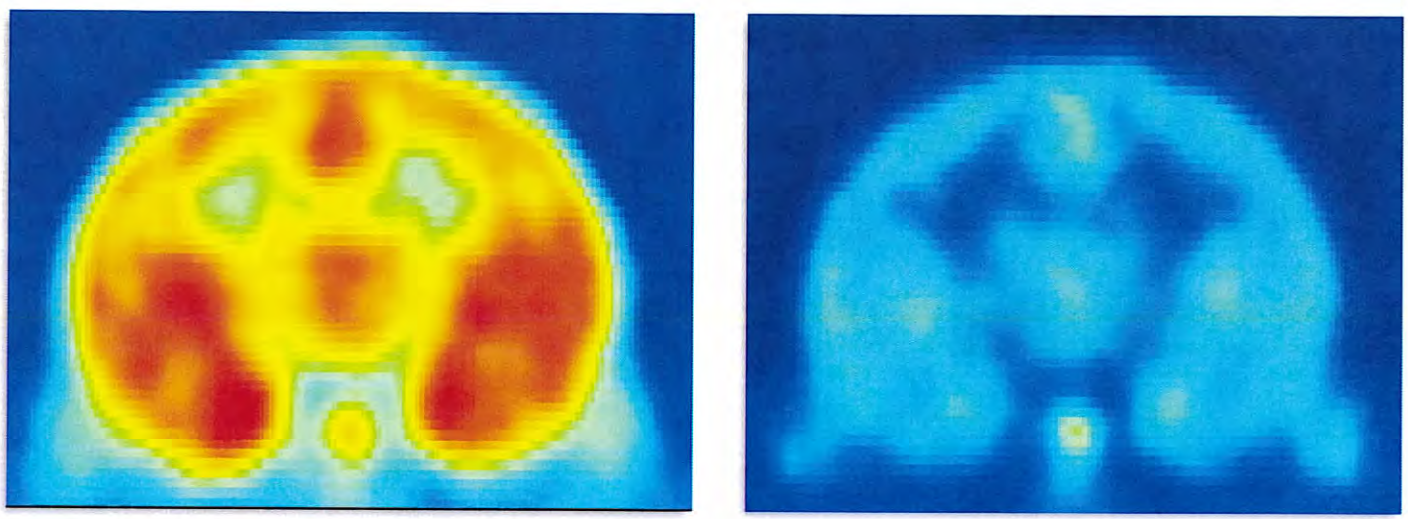
Positron Emission Tomography

- Positron emission tomography (PET) is a noninvasive molecular imaging modality that allows the detection of radiolabeled molecules in living subjects
- PET imaging is used to perform target engagement (TE) studies by quantitatively characterizing the binding of therapeutic candidate molecules in the central nervous system



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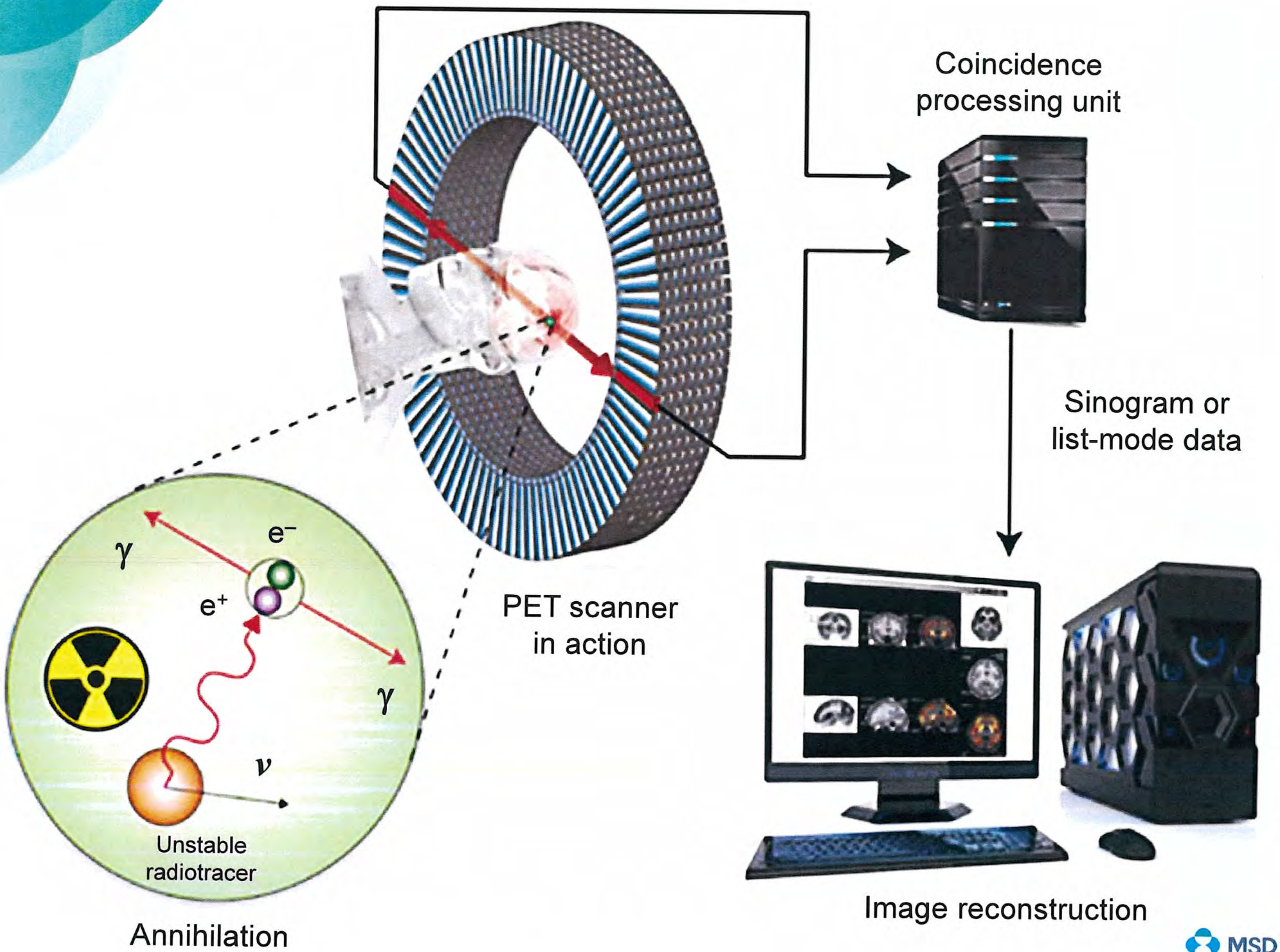
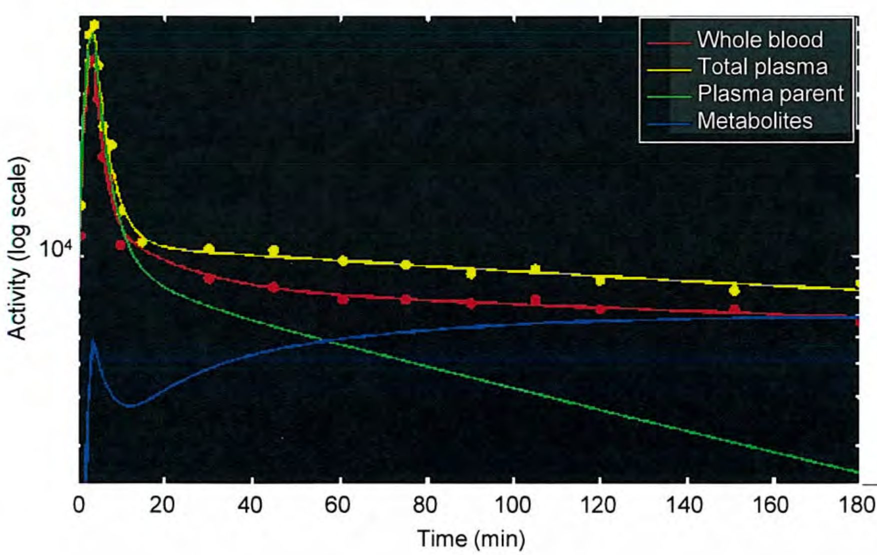
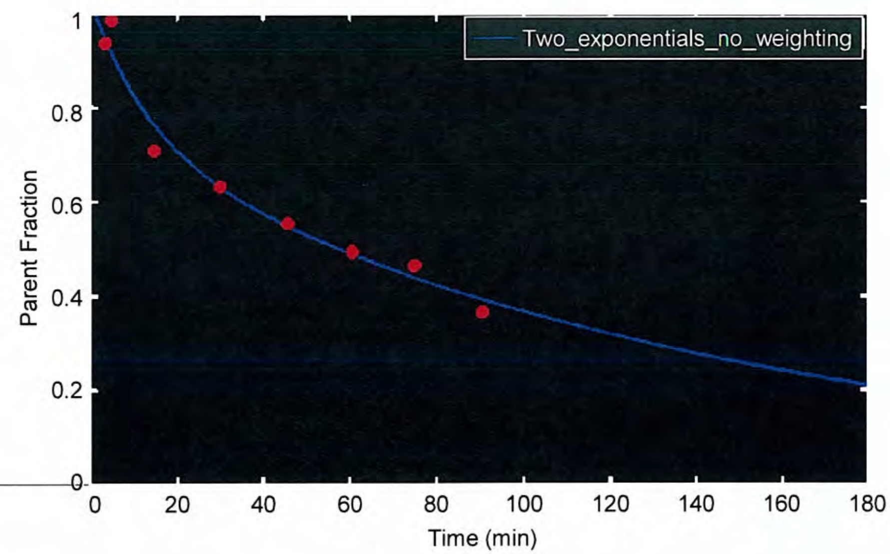

Coincidence
processing unit
Sinogram or
list-mode data
PET scanner
in action
γ
e⁻
e⁺
γ
ν
Unstable
radiotracer
Annihilation
Image reconstruction

Arterial Input Function

- We use rhesus monkeys for our target engagement studies, which often require an arterial input function. Rapid arterial sampling is required for accurate arterial input function and kinetic modeling and analysis
  - The radioactivity concentration in arterial plasma represents the model's input function and is conventionally acquired from rapid measurements of the radioactivity level in arterial blood





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Rhesus Protocol

- Male and female Rhesus Macaques (5-12 kg)
- Ketamine 10 mg/kg IM, followed by IV catheter placement in lower saphenous regions
- Induction with Propofol is 5 mg/kg IV, maintained at 0.4mg/kg/min as a continuous infusion. Animals are intubated and maintained on ventilated oxygen/air gas mixture at approximately 10 cc/kg/breath and 23 respirations per minute. Body temperature is maintained with ventral and dorsal K-module heating pads. General fluid therapy is maintained with 10 mL/kg/hr Lactated Ringer's IV throughout all scanning procedures
- HR, RR, SpO_2, ET CO_2, NIBP, and Temp are recorded throughout all procedures
- Imaging procedures run from 90-180 minutes

- *Anesthesia protocol is intended to keep subject in light plane of anesthesia in order to most closely mimic response of a conscious human. This can be a challenge…*

Manual Sampling Protocol

- Arterial catheter is placed in lower saphenous area, popliteal artery

- Imaging scanner is started and radiotracer is injected over 2 min via syringe pump, IV.
- At the start of radiotracer injection, arterial samples are collected in heparin at 15, 30, 60, 90, 120, and 150 sec (150 µL each x 6 = ~1.0 mL) for counts only
- Arterial samples are also drawn at 3, 3.5, 5, 15, 30, 45, 60, 75, and 90 min (1,000 µL each x 9 = ~9 mL) for plasma metabolites and counts
- At each time point, 20 µL of whole blood and 20 µL of plasma are measured in gamma counter for radioactivity
- All samples are manually time stamped for accuracy

- *These studies are laborious and require 2 physiologists. An automated method has been discussed for many years…*

Pros and Cons of Automation

- **Advantages**
  - Only one physiologist required
  - Reduces handling of nhp blood and radioactive exposure
  - Less blood demand (less aspirate, ~40 μL in line)
  - Less syringe cost, prep time, and waste
  - More samples possible (100 μL every 15-20 sec)
  - No human variables, seamless data points across studies
  - No manual time stamping
  - May be used with rodent procedures

- **Disadvantages**
  - More pipetting labor, more samples in first 5 min
  - Maintain unit, calibrate and clean lines
  - Initial cost, but must then compare to salary demand and change of supplies
  - At this time, can't toggle between fast and slow protocols

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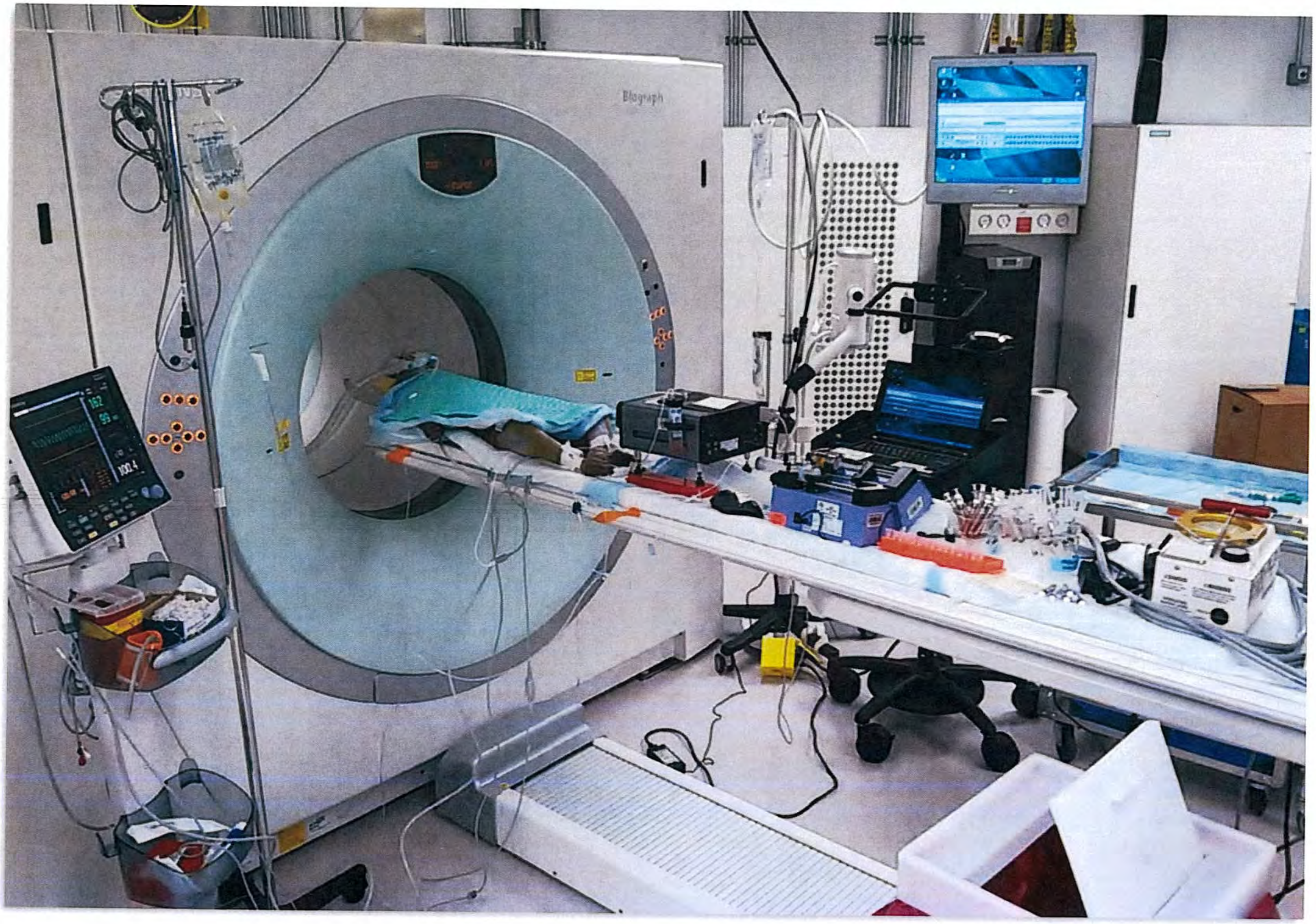
Automated Sampling Validation

- In collaboration with T. Baldini from Instech, an automated blood system (ABS) was modified for small-volume rapid sampling and compared to the manual "gold standard" method
  - Bacteriology studies performed
  - ABS2 system was tested for various timing, volumes, tubing materials, and radioactive affinity (ex vivo and then in vivo)

- ABS time points were matched to manual sampling time points
  - 100 µL collected at 15, 30, 60, 90, 120, 150 sec, 3, 3.5, 5 min
  - 800 µL samples collected at 6, 15, 30, 45, 60, 75, and 90 min

Dual Arterial ABS and Manual Study



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Dual Arterial ABS and Manual Study

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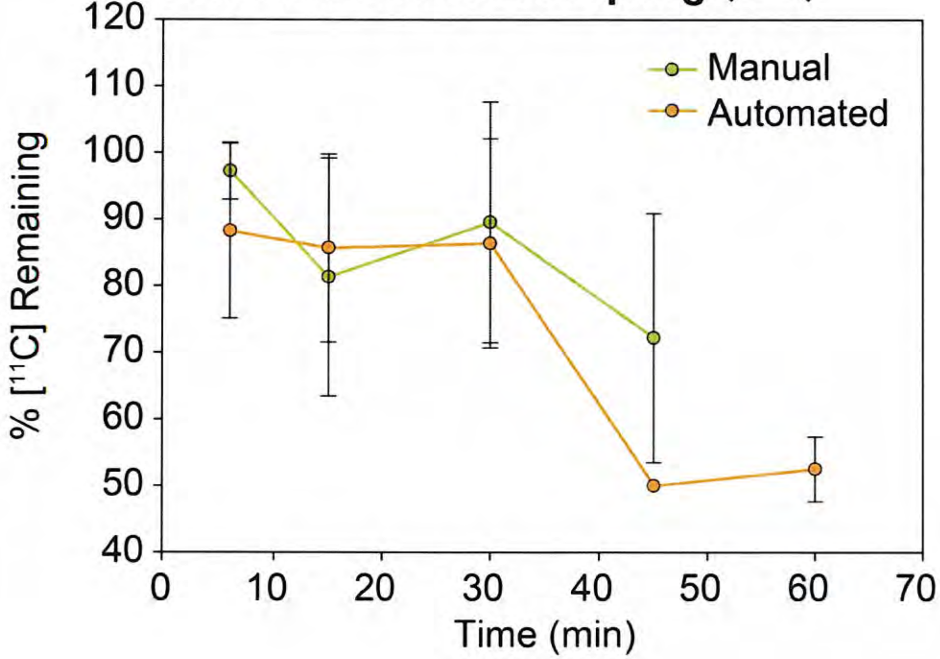
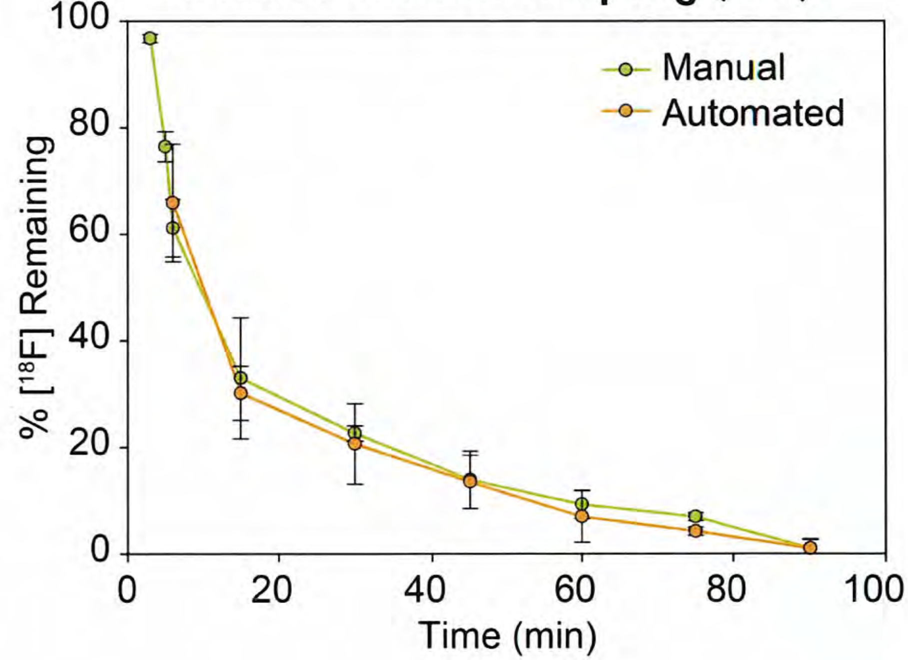
Metabolism of [^{11}C] Tracer A in Rhesus monkey plasma — manual vs automated blood sampling (n=3)

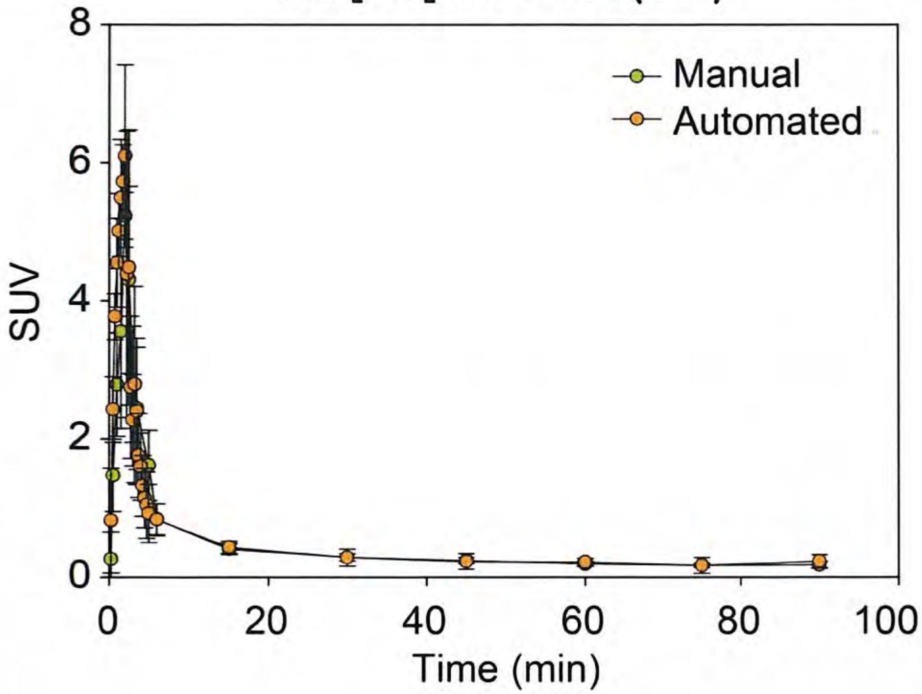


Metabolism of [^{18}F] Tracer B in Rhesus monkey plasma — manual vs automated blood sampling (n=3)

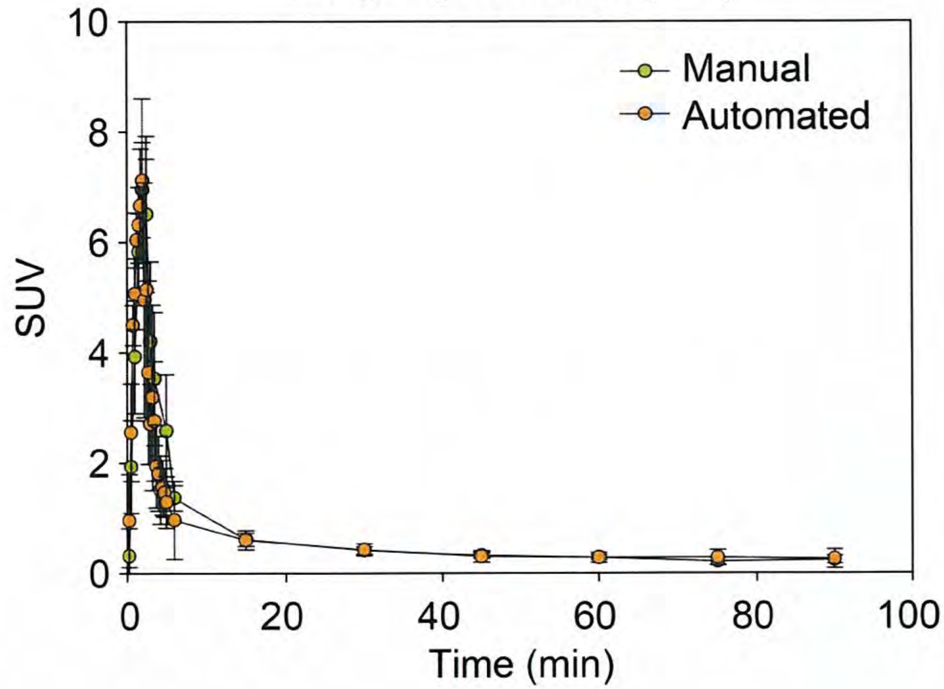


SUV and metabolism data - K. Riffel

Whole-blood SUVs – manual vs automated blood sampling for [^{11}C] Tracer A (n=3)



Plasma SUVs – manual vs automated blood sampling for [^{11}C] Tracer A (n=3)



SUV and metabolism data - K. Riffel

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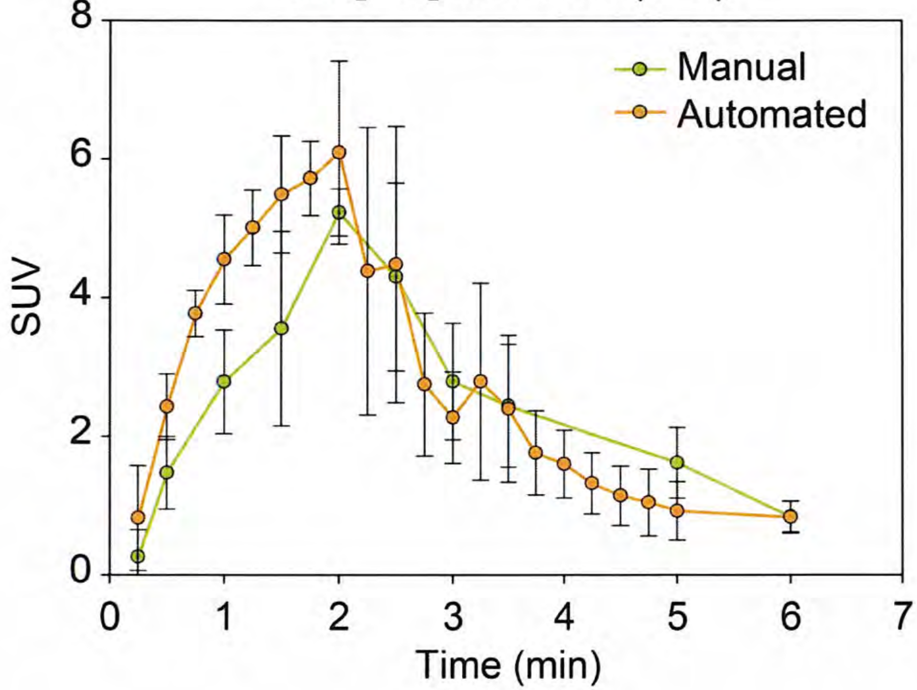

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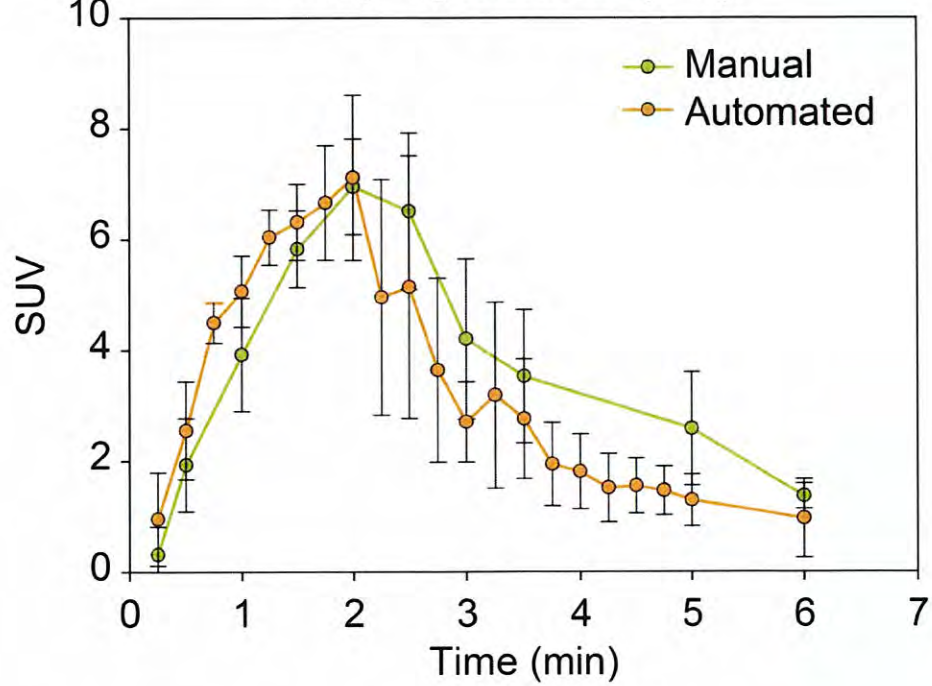

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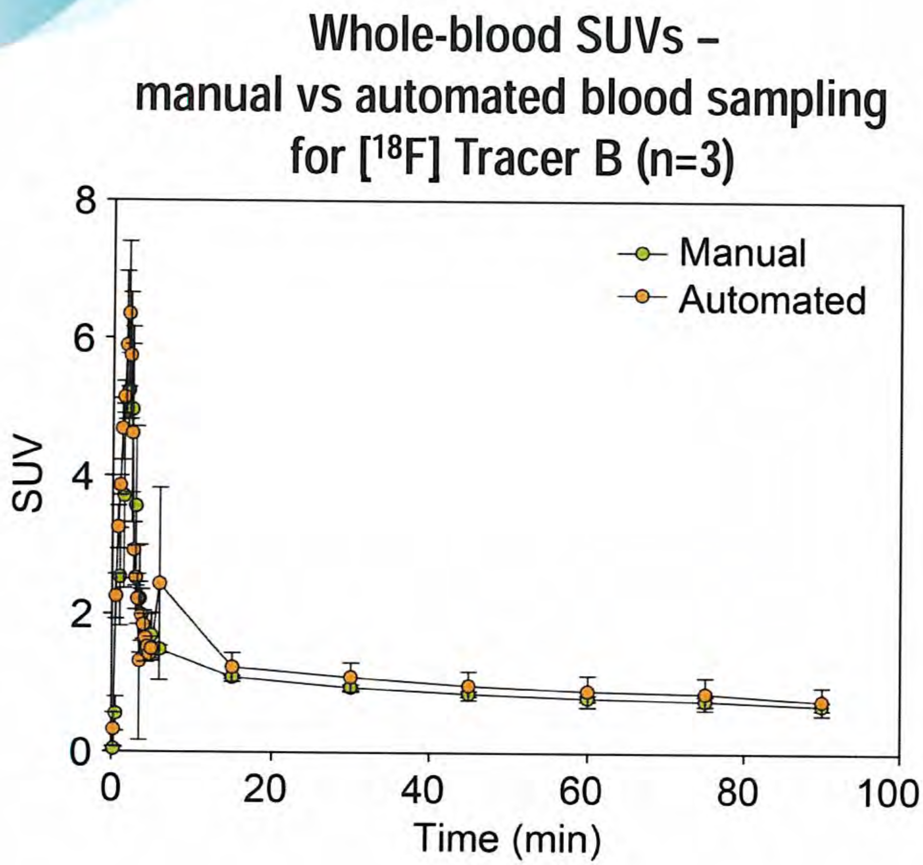
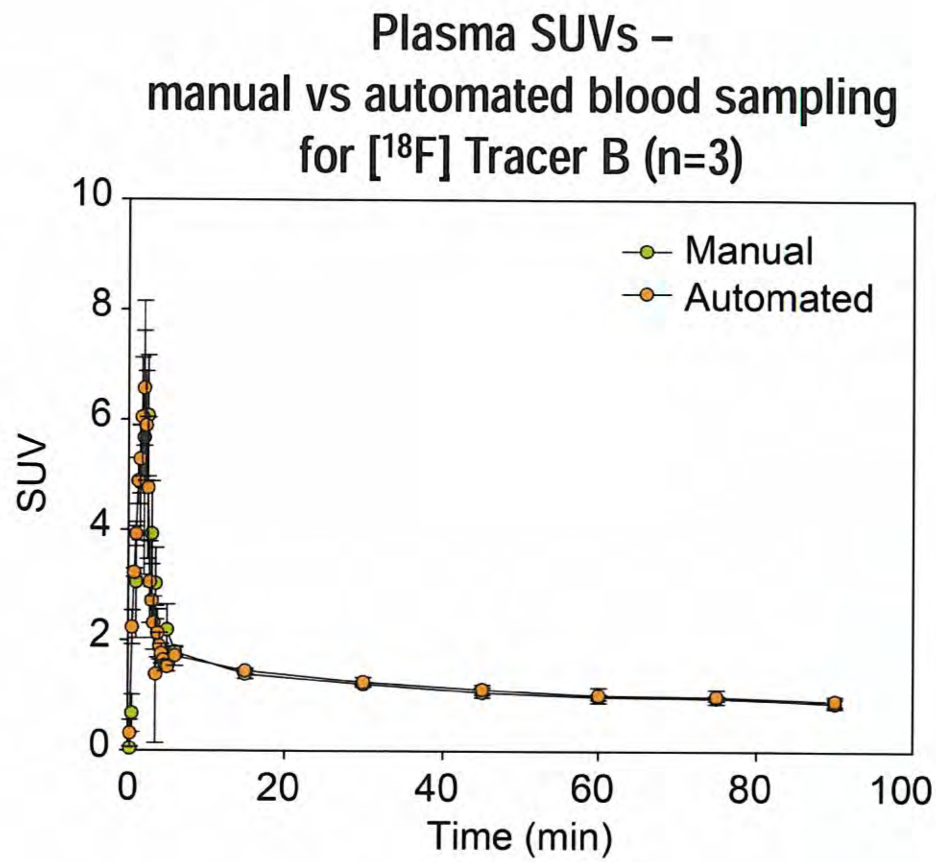
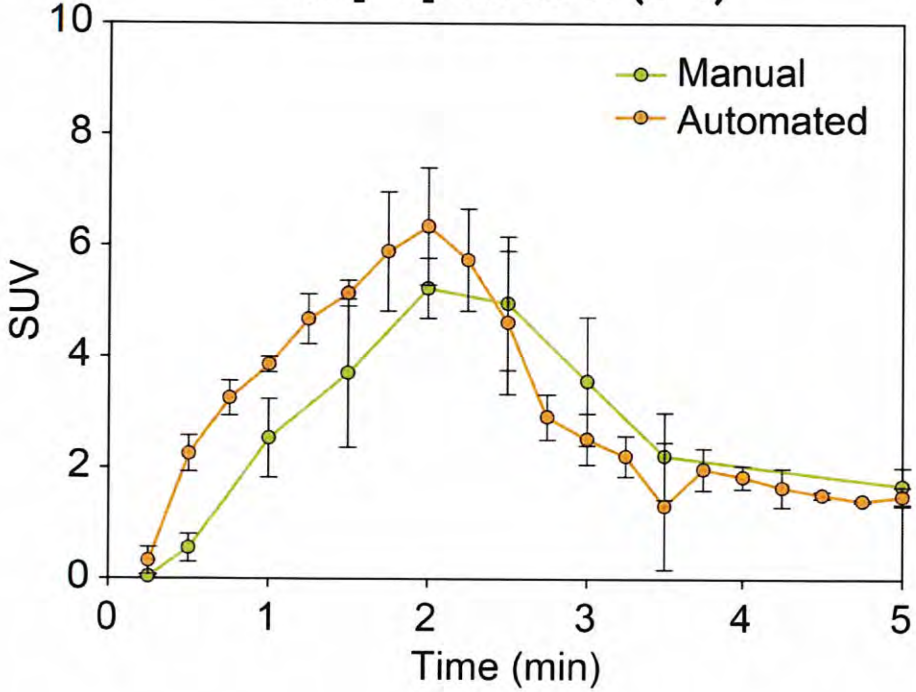


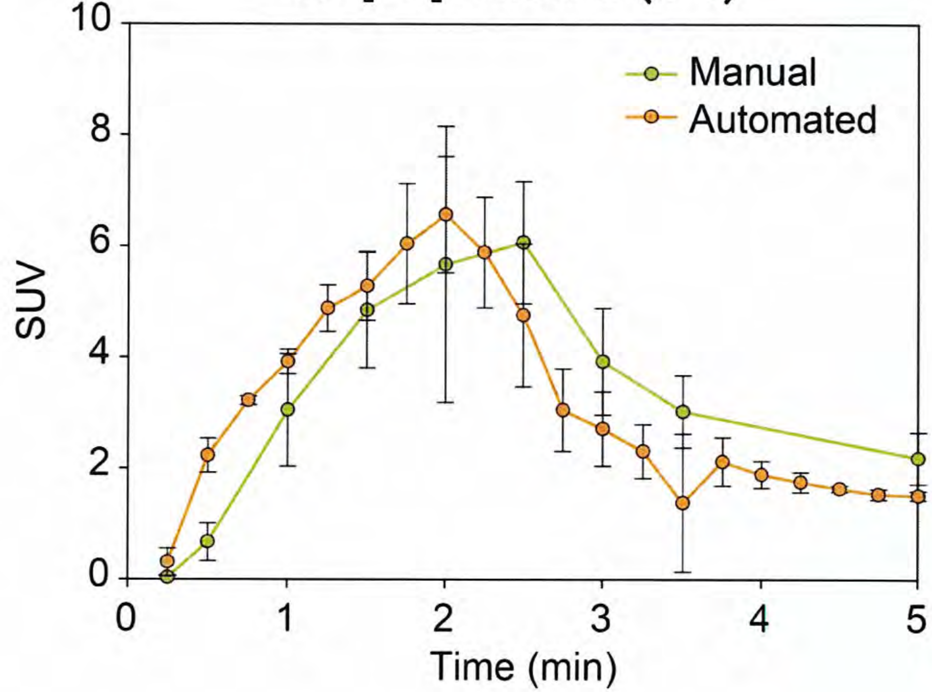


SUV and metabolism data - K. Riffel

Whole-blood SUVs – manual vs automated blood sampling for [^{18}F] Tracer B (n=3)



Plasma SUVs – manual vs automated blood sampling for [^{18}F] Tracer B (n=3)



SUV and metabolism data - K. Riffel

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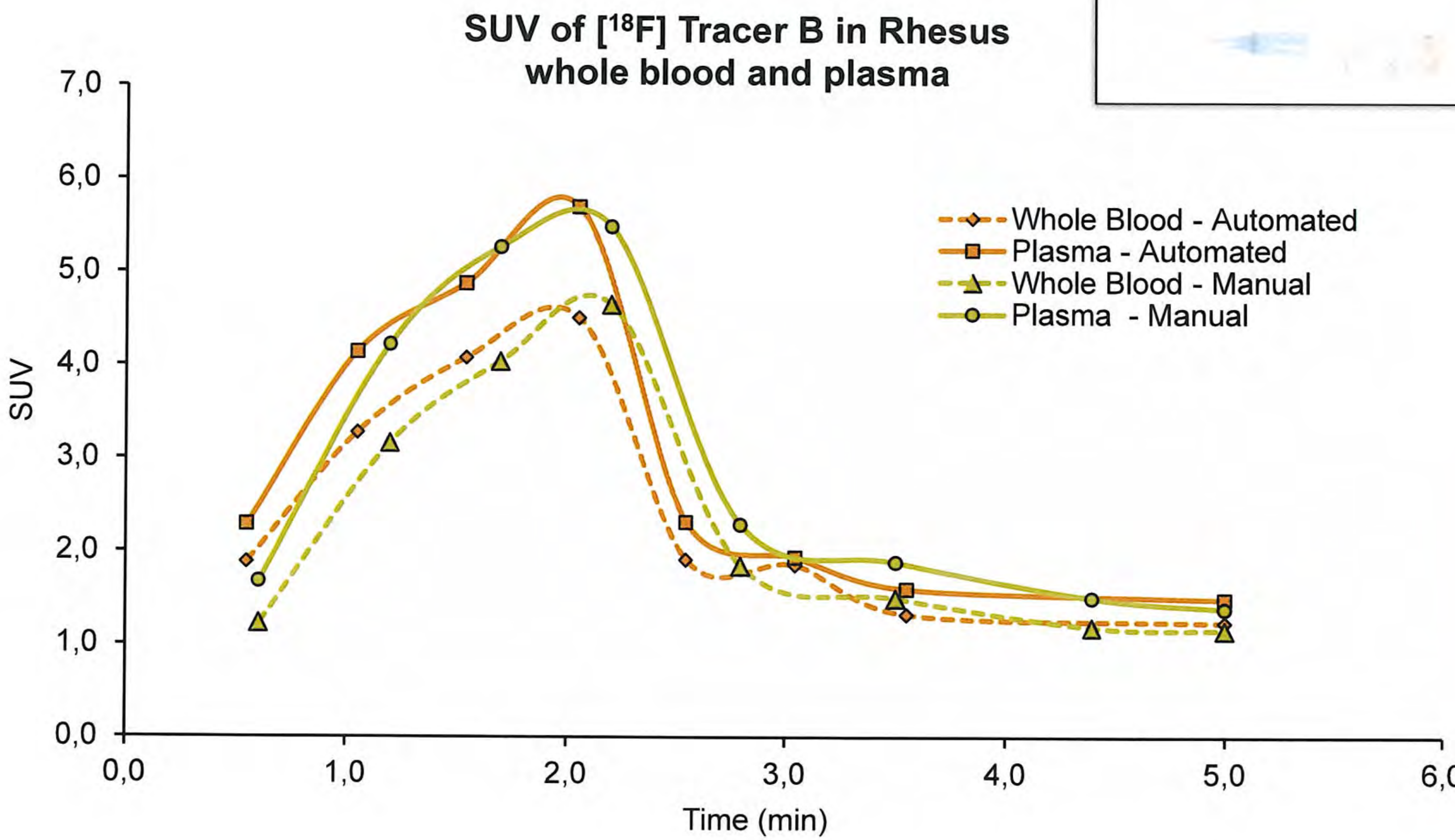
Dual Arterial Comparison Study With Pinport Technique



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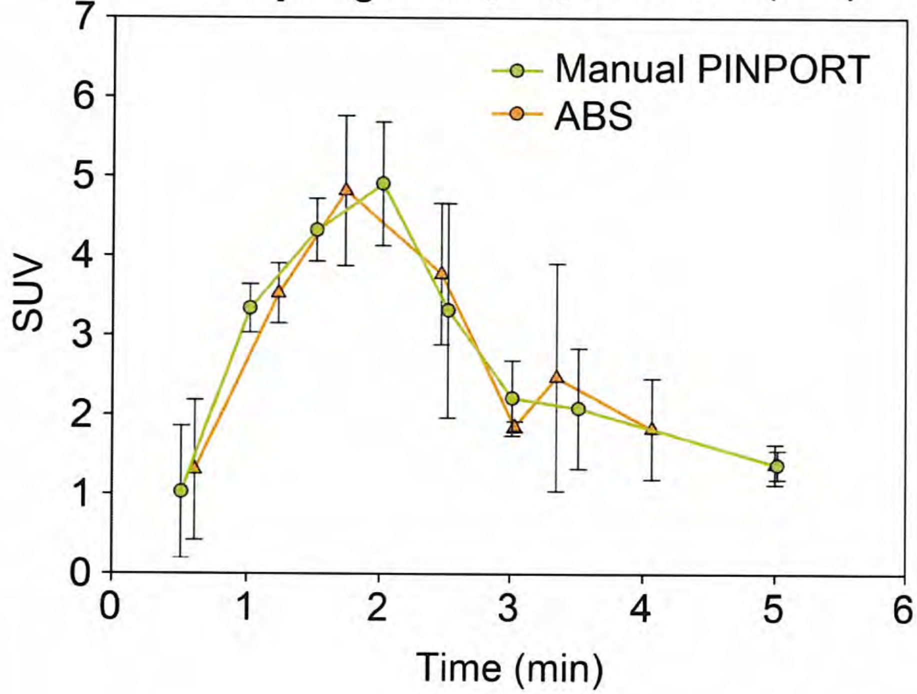
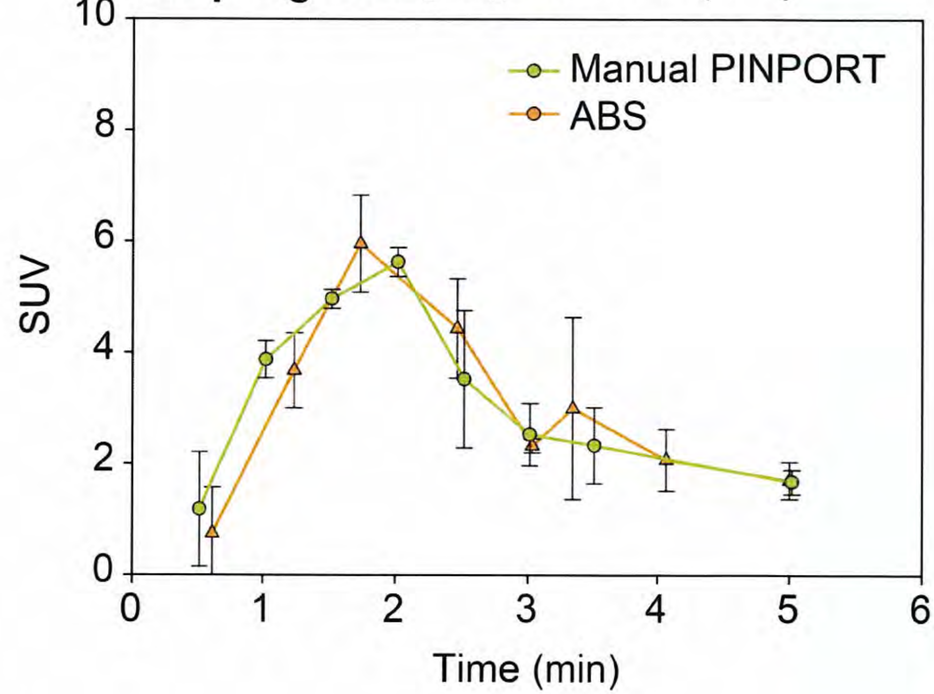
Whole-blood SUVs – PINPORT manual vs automated blood sampling with [18F] Tracer B (n=3)



Plasma SUVs – PINPORT manual vs automated blood sampling with [18F] Tracer B (n=3)



SUV and metabolism data - K. Riffel

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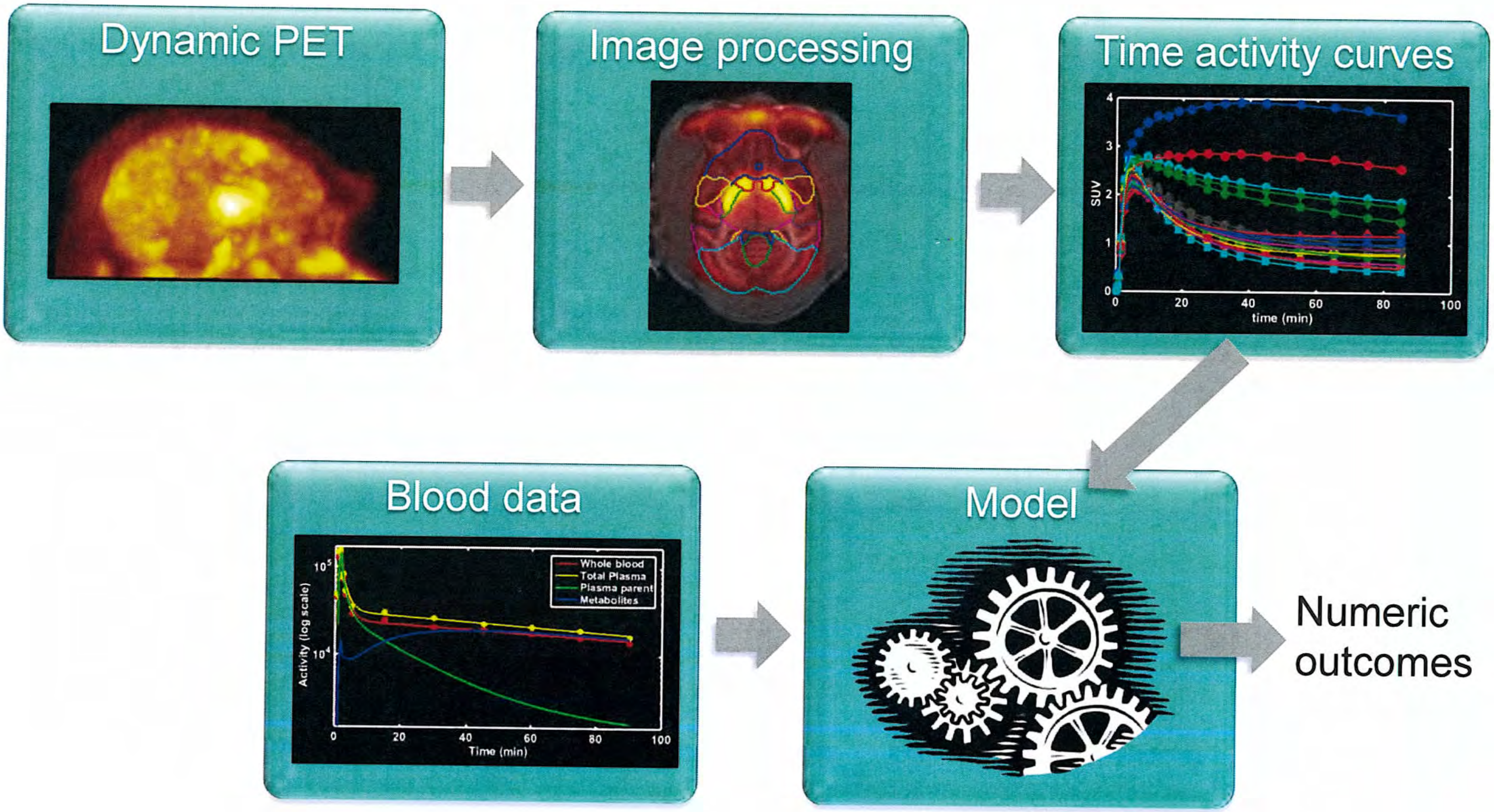
PET Quantification



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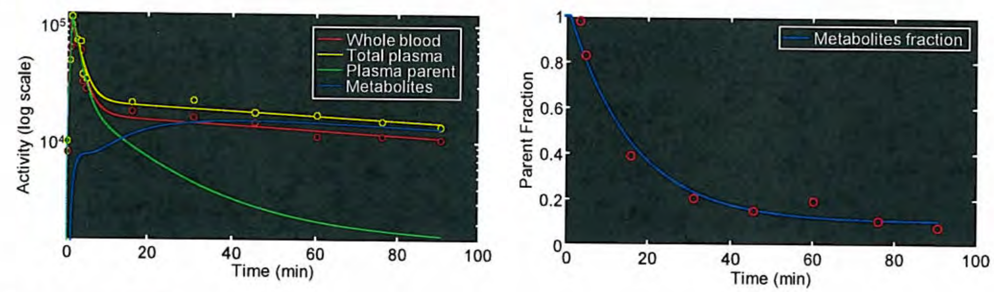
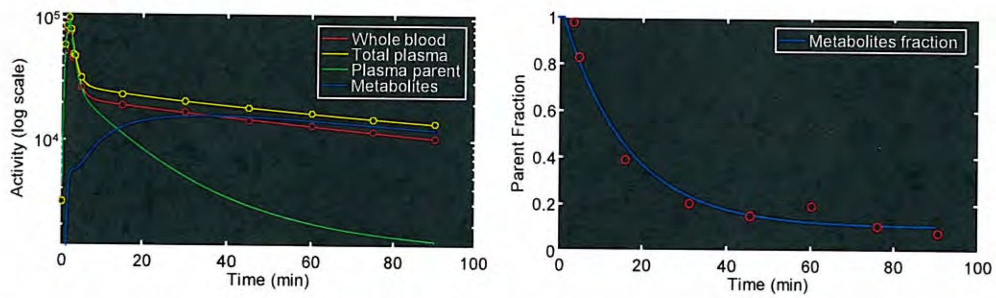
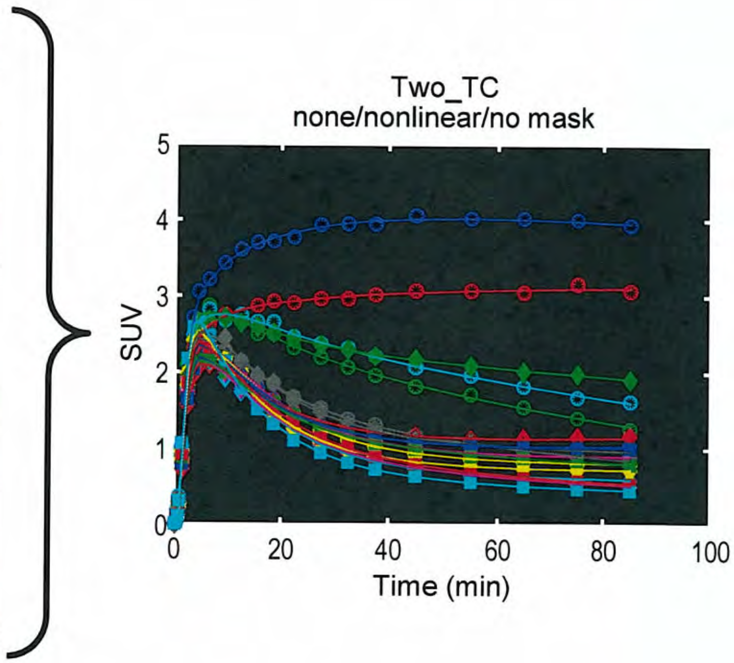
Arterial Input Function, Time Activity Curve, and Parent Fraction Comparison Analysis by C. Salinas

Manual

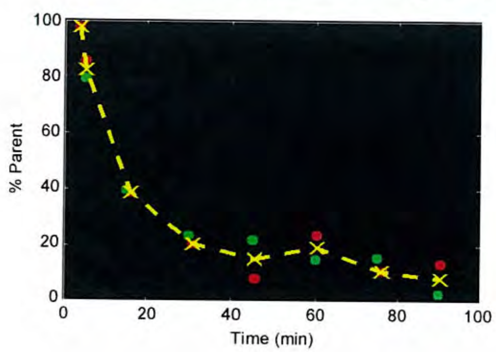


Automatic





Parent fraction comparison



- Automatic blood sampling produces volume of distribution values that are equivalent to those obtained with manual sampling

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SUV and Metabolite Statistics Summary by S. Wang

- Intraclass correlation (ICC) is a primary quantitative measure of reproducibility; it is one of the most widely used metrics to describe how well the paired measures resemble each other (in our case, manual and automated measurements at one time point for a specific subject). ICC>0.5 as strong reproducibility

- **Whole-blood SUVs** were reproducible: ^{18}F ICC = 0.85 and ^{11}C ICC = 0.82
- **Plasma SUV** showed good reproducibility: ^{18}F ICC = 0.87 and ^{11}C ICC = 0.86

- Metabolite-corrected-plasma SUV alone had good reproducibility: ^{18}F ICC = 0.88 and ^{11}C ICC = 0.89. The combined metabolite-corrected-plasma SUV had good reproducibility also: ^{18}F ICC = 0.89 and ^{11}C ICC = 0.86.
- Automated metabolism samples showed great reproducibility compared to the manual samples: ^{18}F ICC = 0.97 (partial ICC = 0.67) and ^{11}C ICC = 0.97 (partial ICC = 0.96). *The ICCs might be inflated by the time-effect in the data; we also need to consider using partial correlation approaches. The reproducibility tests with partial correlations also showed that all the endpoints have good reproducibility.*

- **In summary, all the endpoints of the automated sampler showed great reproducibility**

Conclusions and Next Steps

- The ABS SUVs, metabolites, TAC curves, and fraction measurements were all comparable and well within range of the manual measurements
- A small dilution factor was discovered in the manual method. The pinport comparison studies explained the cause of sample concentration differences
- This innovation significantly improves **efficiency** and **safety**:
  - Increases our throughput from a two-man study to a one-man study
  - Reduces radioactive and biological exposures to personnel
  - Reduces blood volume demand from the animals
  - Allows for more sample time points per study
- The ABS is being rolled out to new PET projects in 2015

Thank You, Gracias, Danke, Merci...

K Riffel

C Salinas, A Joshi

T Baldini @ Instech

M Holahan, H Haley, M Purcell, D Posavec

S Wang

DE González Trotter

MSD