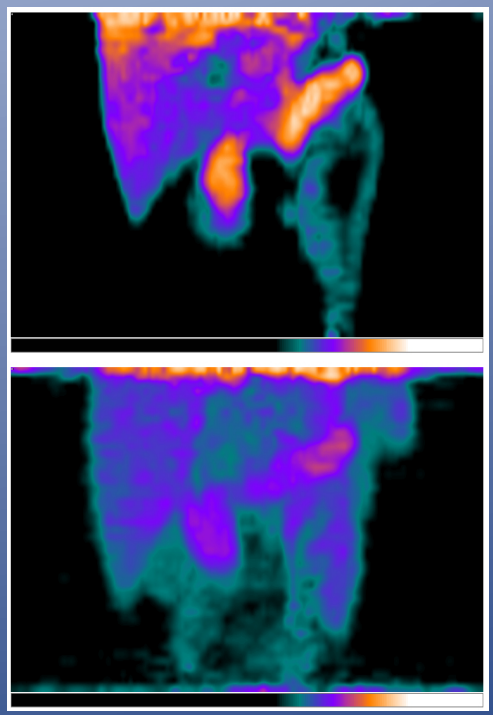
In Vitro Evaluation of Non-Specific Binding of the Candidate Beta Cell Mass PET Probe (+) 18F-FP-DTBZ.

P. Harris

Naomi Berrie Diabetes Center and
Department of Radiology
Columbia University Medical Center



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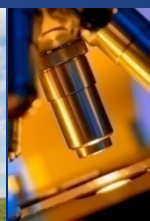

Summary

- The vesicular monoamine transporter Type 2 (VMAT2) is a candidate beta cell mass (BCM) marker that can be evaluated non invasively by PET using the radioligand (+) 18F-FP-DTBZ

- Immunohistochemistry studies show that VMAT2 faithfully tracks insulin staining in controls, T2DM and T1DM pancreas tissue.

- Cross sectional studies of healthy human volunteers and subjects with long standing type 1 diabetes, predicted to have little or no beta cell mass based on metabolic measurements show significant differences in outcome measure, but there is a background signal where there should be little or no beta cell mass.

- Can this background be measured *in vitro* by other techniques so as to better understand its cause.

- Human Studies.




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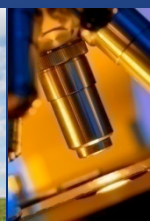
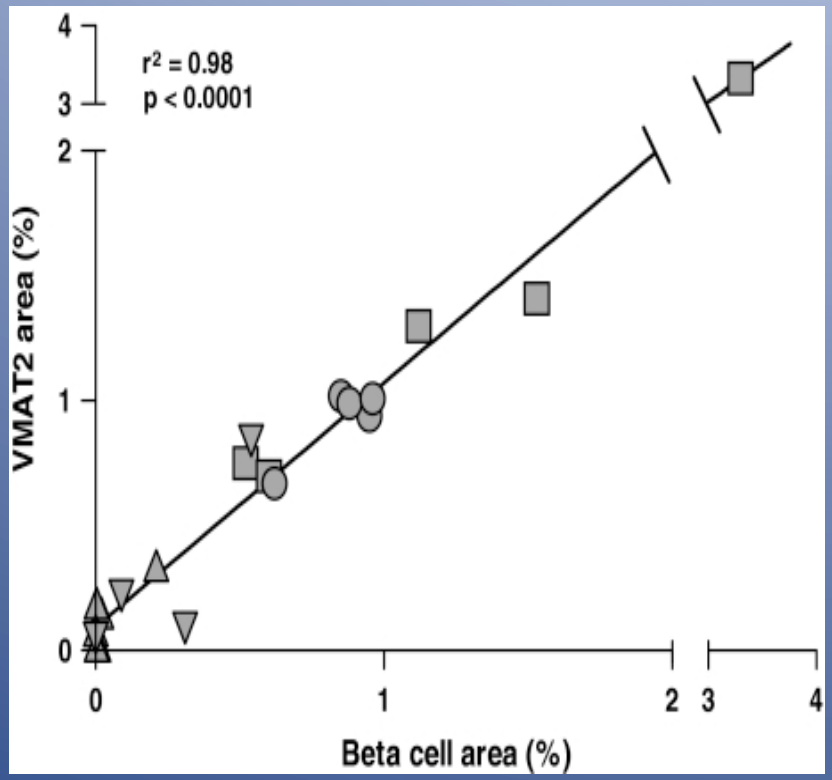
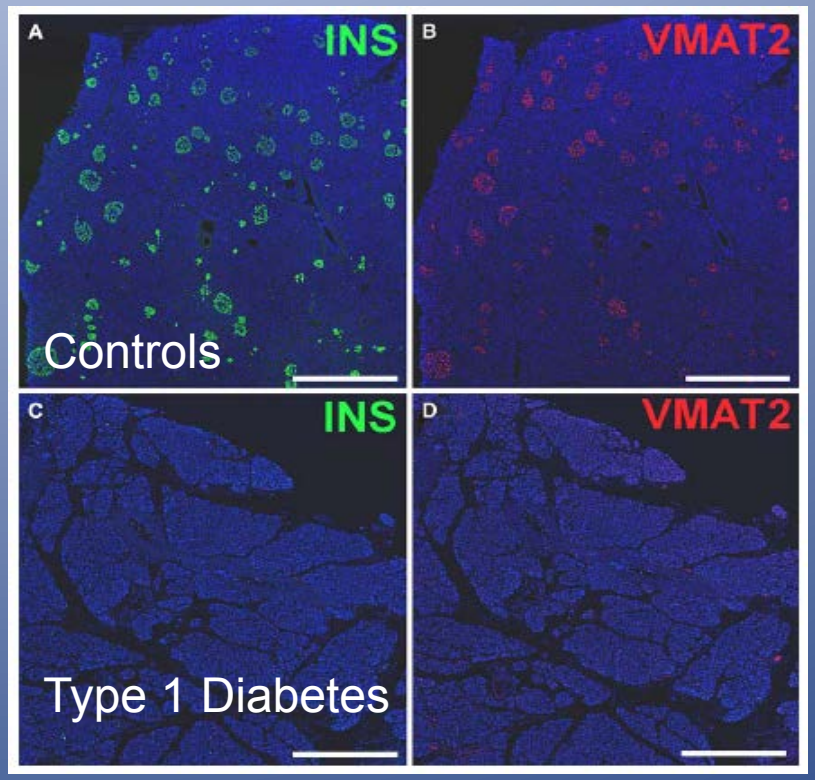


Expression of VMAT2 biomarker faithfully represents disease state





VMAT2 expression tracks beta cell area and presence of type 1 and type 2 diabetes.

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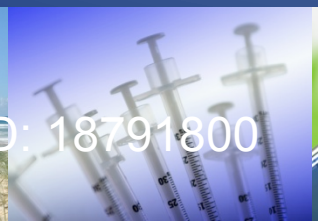

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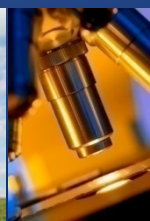


Human cross sectional study of PET based VMAT2 measurement in Controls and T1D patients using [11C] DTBZ.

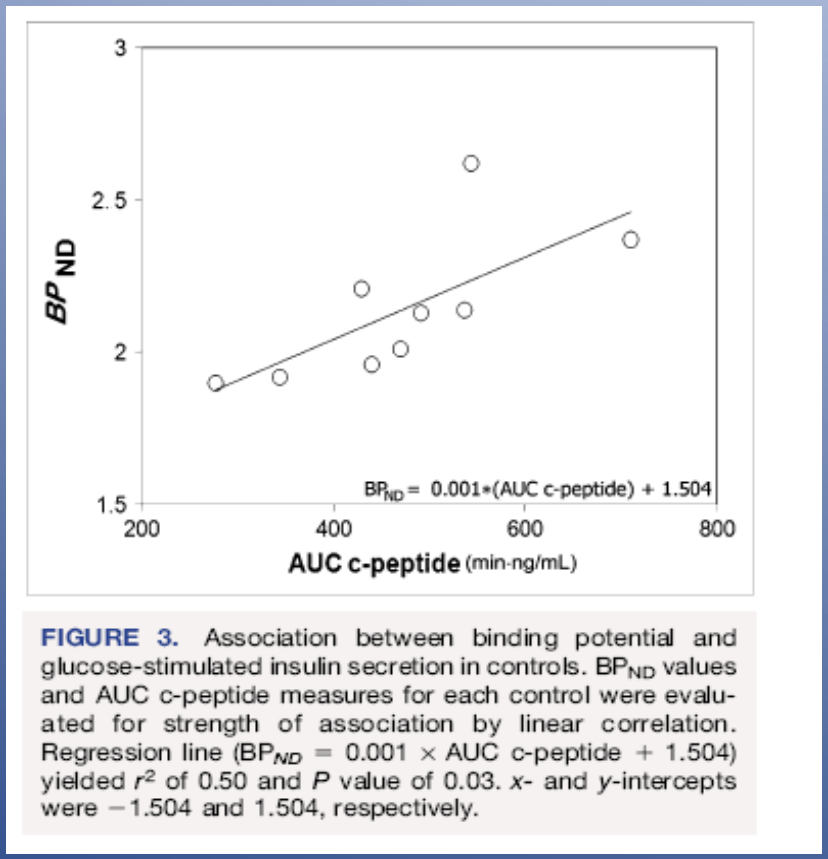
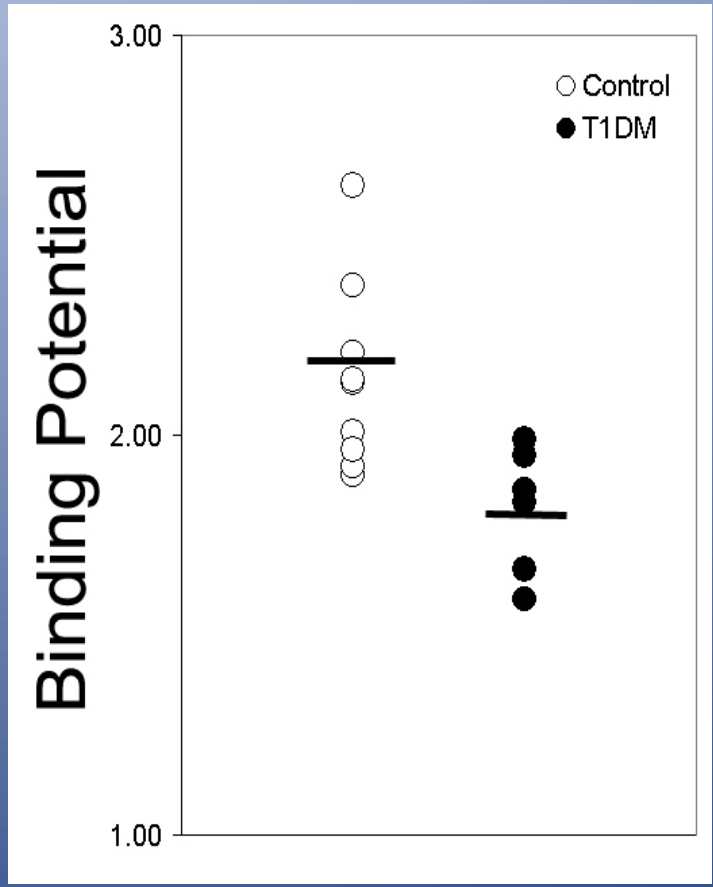


FIGURE 3. Association between binding potential and glucose-stimulated insulin secretion in controls. BP_{ND} values and AUC c-peptide measures for each control were evaluated for strength of association by linear correlation. Regression line (BP_{ND} = 0.001 × AUC c-peptide + 1.504) yielded r^2 of 0.50 and P value of 0.03. x- and y-intercepts were −1.504 and 1.504, respectively.



(Goland et al [11C]DTBZ PET imaging of the pancreas in subjects with longstanding type 1 diabetes and healthy controls. Journal of Nuclear Medicine. 2008.)

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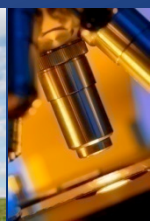
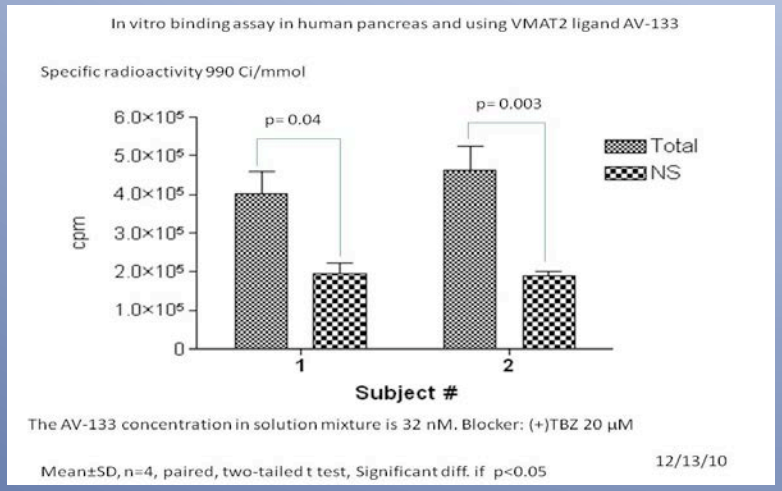
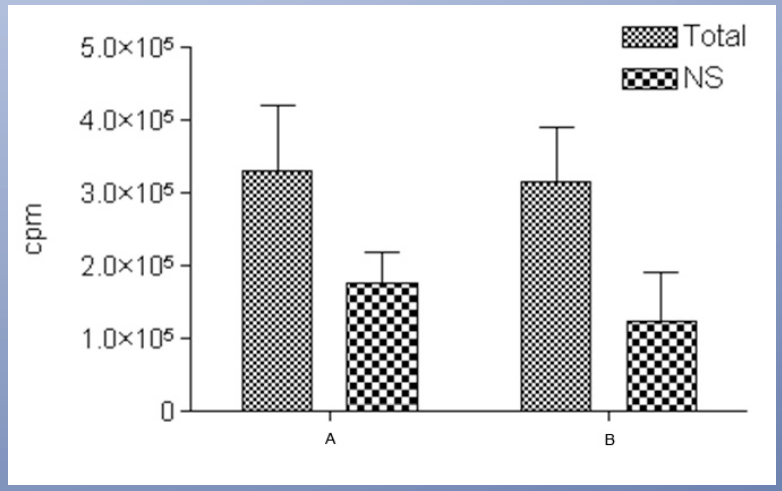
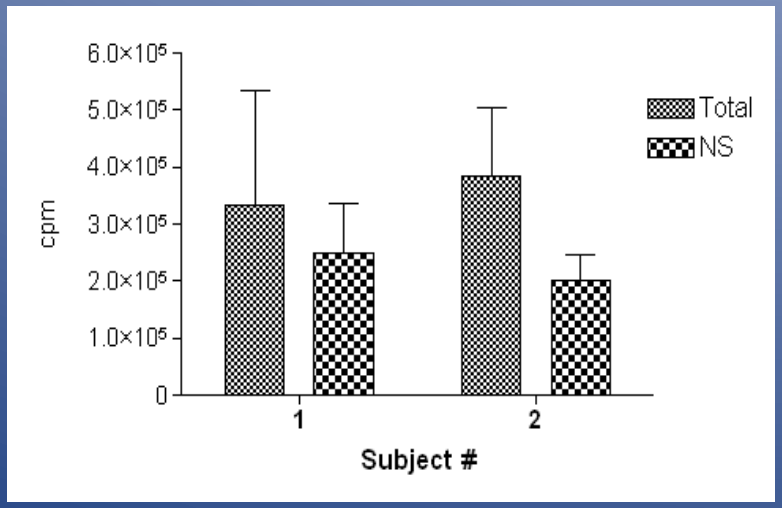
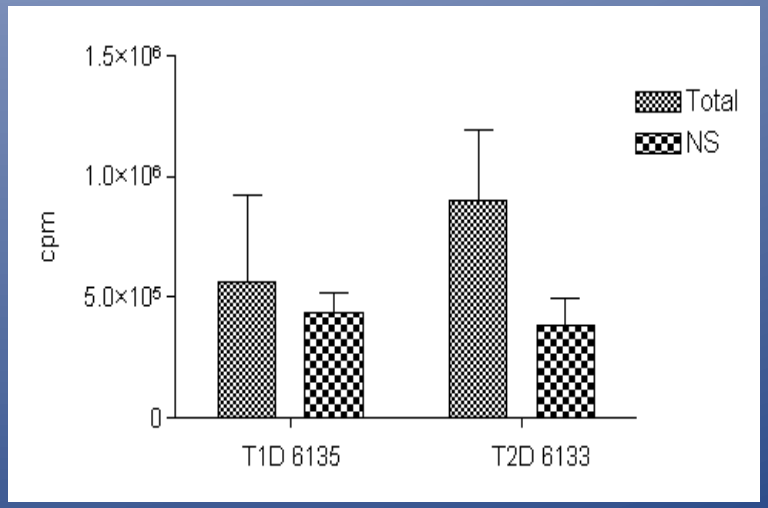


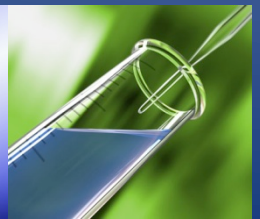
Evaluation of Non Specific Binding of PET probe in Human Pancreas Homogenates











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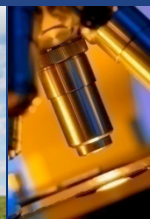
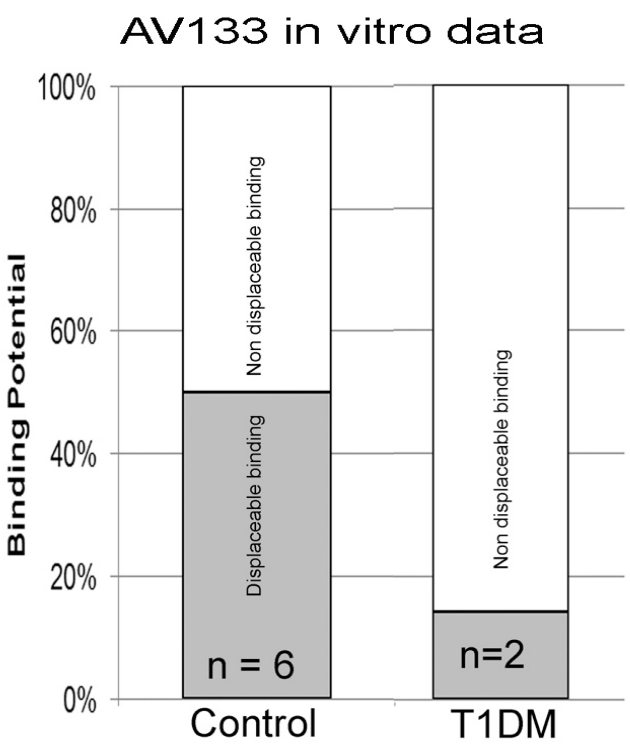
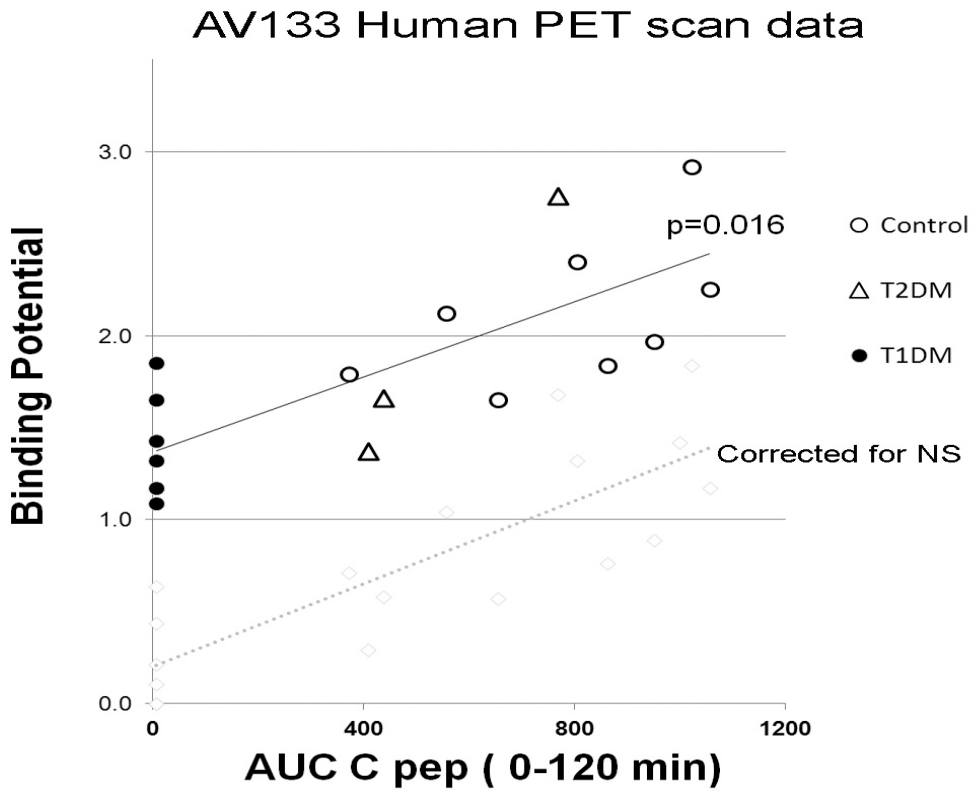


Correction of in vivo data using non specific binding estimates from in vitro experiments





This correction must be validated in a human study with (-) [^{18}F]FP-DTBZ

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Summary

1. PET measurements of VMAT2 correlate well with AUC c peptide but T1DM pancreata with no beta cell mass show a significant background PET signal

2. Studies of human pancreas membranes show significant non displaceable binding of the PET tracer (+)18F-FP DTBZ . In vitro studies show non specific binding of the tracer to be about 50% of the total probe binding. Non specific binding of the tracer appears greater in T1DM pancreas membranes. This non specific binding is probably responsible for the background signal observed in vivo.

3. Evaluation of non specific binding of tracer needs to be evaluated in vivo using (-) 18F-FP DTBZ. If non specific binding is variable among individuals or changes during disease progression, accurate VMAT2 quantitation may require imaging with both (+) and (-) 18F-FP-DTBZ.

4. This $ 5,000 clinical PET imaging method seems to be able to non invasively distinguish a healthy control pancreas from a pancreas of a long term type 1 diabetes patient in a cross sectional study…most of the time and almost as well as an $ 100 metabolic test.




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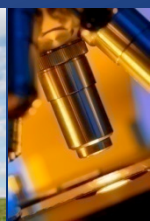
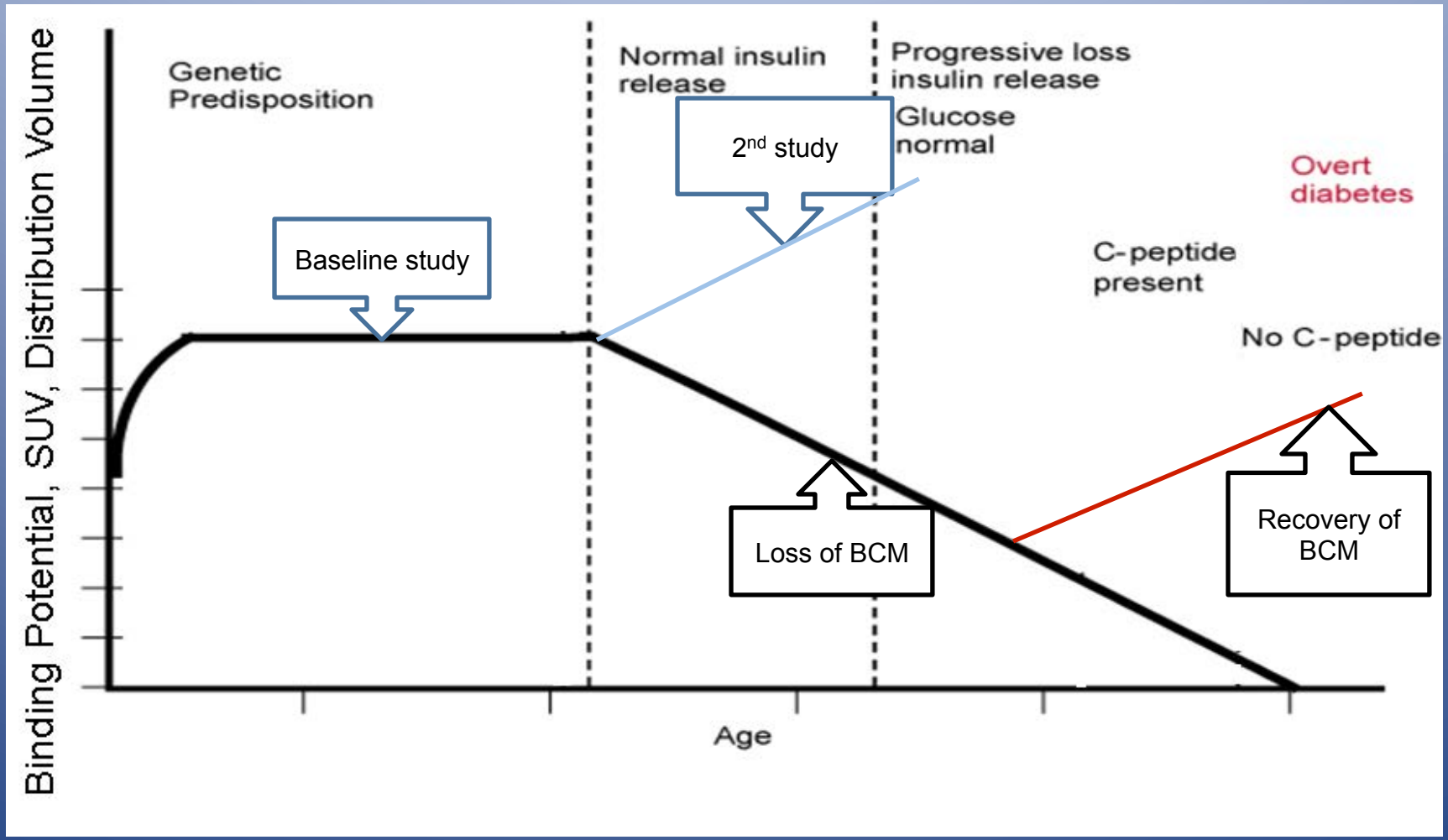
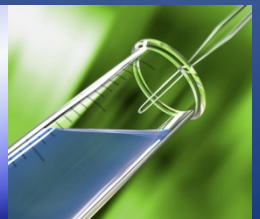


Changes in Imaging outcome measure will be the clinically relevant test.







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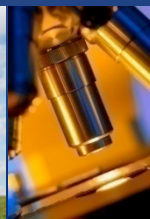

Summary continued

5. The difficulties associated with cross sectional studies may be lessened in serial longitudinal studies where changes in probe uptake are used as the outcome measure

    i. Individual variability of beta cell mass is accounted for
    ii. Non specific binding of the probe is compensated

6. The sensitivity of measure of change in uptake will depend on the test retest variability and the magnitude of non displaceable binding




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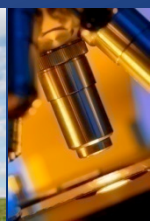

Collaborations and Support

- Columbia Radiology
- Masanori Ichise

- Naomi Berrie Diabetes Center
- Matthew Freeby
- Patricia Kringas
- Robin Goland
- Rudolph Leibel

- Columbia Endocrinology
- Antonella Maffei
- Norman Simpson

- Yale PET Center
- Gary Cline
- Rich Carson

- Hillblom Islet Research Center UCLA
- Peter Butler
- Yoshifumi Saisho

- NIH NIDDK
- JDRF
- nPOD
- NDRI
- Leona M. and Harry B. Helmsley Charitable Trust

- Conflict of Interest Disclosure

- The authors have licensed IP with
- AVID radiopharmaceuticals who supply
- 18F-FP-DTBZ for many of the studies cited.




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