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## Developing New Imaging Methods for Acute Stroke

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## Clinical Need for More Imaging

FACE. ARMS. SPEECH. TIME.

Stage	Non-stroke (%)	Stroke (%)
Ambulance	178	41
Primary Care	216	63
ER	93	27

Harbison et al. Stroke. 2003;34:71-76

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## Stroke: Clinical Syndrome, Pathologically Heterogeneous

Haemorrhage	Ischaemic	Non-Stroke

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## "Clot-Busting" Drugs Save Brain

Brain "at risk"

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## Critical Time-Dependence of Thrombolysis

ECASS 3

Window	1.5h	1.5-3h	3-4.5h	4.5-6h
Adjusted odds ratio	2.8	1.5	1.4	1.2
Absolute Benefit	12%	13%	5%	1%
NNT	8	8	20	100

Hacke et al. N Engl J Med 2008;359:1317-29  
 Hacke et al. Lancet 2004; 363: 768-74

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## How Many Patients Could Benefit?

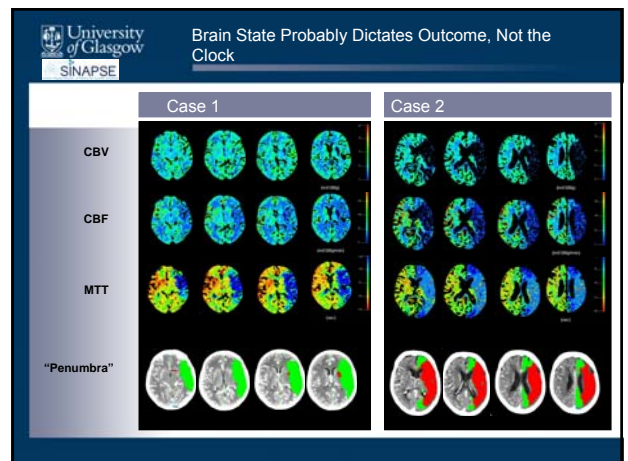
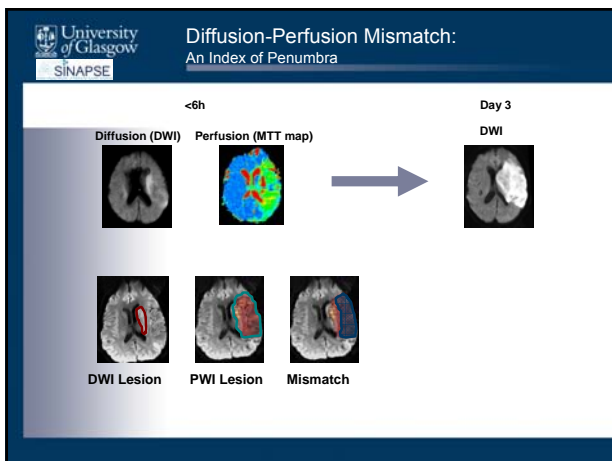
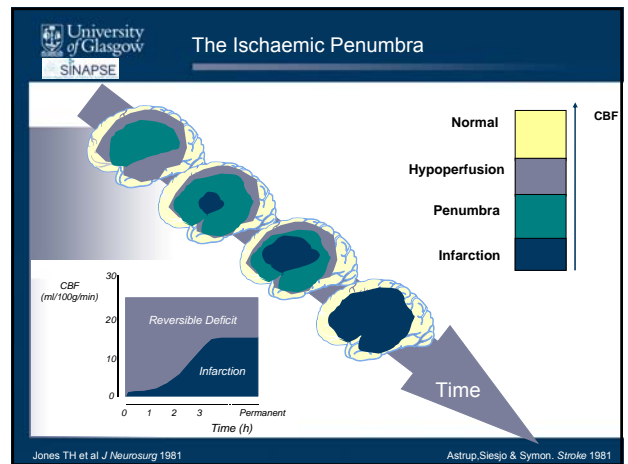
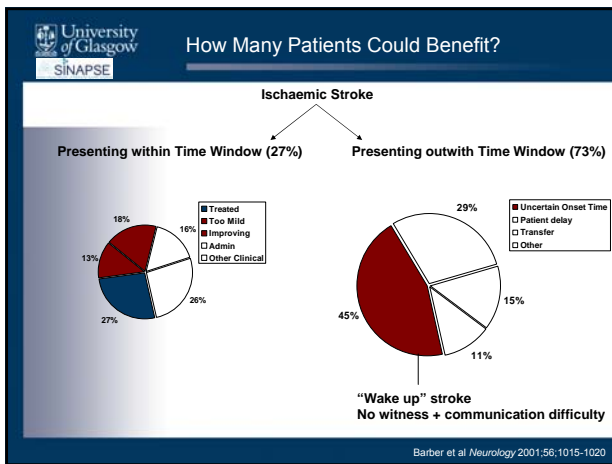
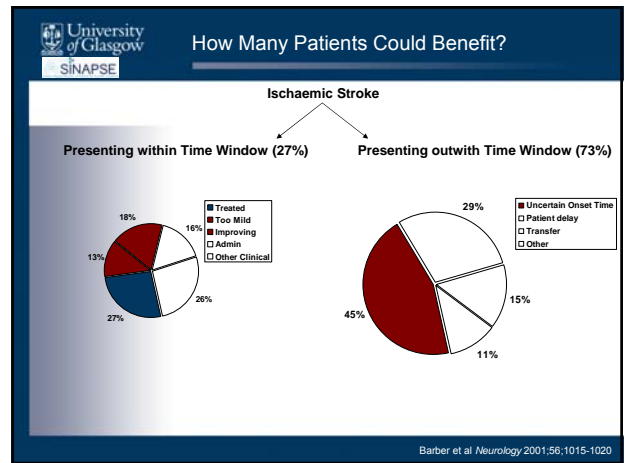
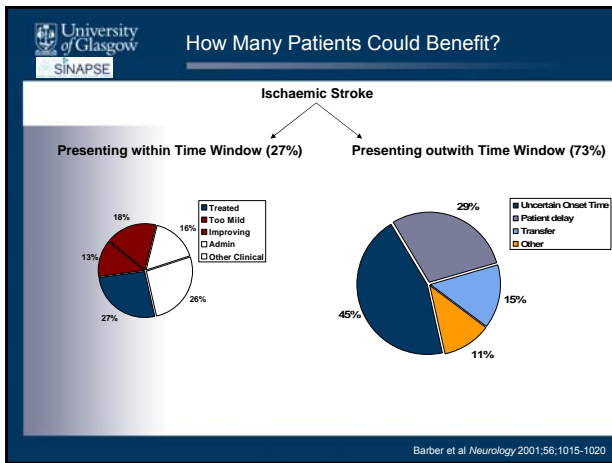
Ischaemic Stroke

Presenting within Time Window (27%)

Presenting outwith Time Window (73%)

Category	Percentage
Treated	18%
Too Mild	13%
Improving	27%
Admin	16%
Other Clinical	26%
Uncertain Onset Time	29%
Patient delay	45%
Transfer	15%
Other	11%

Barber et al. Neurology 2001;56:1015-1020



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### The Downside of Reperfusion: Intracerebral Haemorrhage

NINDS SICH Cases

Stroke 1997;28:2109-2118

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### Can Imaging Predict Risk of SICH?

DEFUSE: "Malignant Profile"

- Defined after DEFUSE interim analysis
- DWI volume >100ml and/or PWI volume >100ml and  $T_{max} >8s$
- Poor clinical outcome
- High risk (50%) of SICH with early reperfusion

Albers et al Ann Neurol 2008;60:508-17.

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### Does Imaging Selection Improve Clinical Outcomes?

Study	Imaging Selection	0-1	2	mRS 3-5	6	n
Pooled RCTs	Placebo 0-3h	29	11	43	17	465
	Alteplase 0-3h	42	7	33	18	463
Hamburg Heidelberg Cologne Frankfurt Barcelona	MRI 3-6h	40	7.8	38.9	13.3	174
	MRI <3h	37	16.2	35.1	11.7	322
	CT <3h	35.4	14.3	36.6	13.7	714

Schellinger et al. Stroke 2007;38:2640-2645  
Wahlgren et al. Lancet 2007; 369: 275-82

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### Clinical Trial Use: Imaging as a Surrogate Endpoint

	rtPA	Placebo
n	37	43
Lesion Growth (Geometric Mean)	1.24	1.78
Absolute (ml)	4.1	28.7
Reperfusion	19 (56%)	11 (26%)
Recanalisation	14 (74%)	16 (57%)

Davis et al Lancet Neurol 2008;7:299-309.

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### EPITHET: Effect of Reperfusion 3-6h Mismatch Patients

	Reperfusion	No Reperfusion
n	30	47
Lesion Growth	0.79	2.25
Absolute (ml)	-1.0	43.6

Davis et al Lancet Neurol 2008;7:299-309.

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### Problems with MRI Mismatch

ADC values overlap both penumbra and core perfusion defined by PET

DWI lesions are reversible with reperfusion

Guadagno et al. J Cerebral Blood Flow & Metabolism 2004;24:1249-1254

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### Reversibility of DWI with Reperfusion

Pre-Thrombolysis: DWI, ADC, T2, PWI  
Post-Thrombolysis: DWI, ADC, T2, PWI  
Pre: [DWI scans]  
Post: [DWI scans]

Kidwell et al. *Ann Neurol* 2000;47:462-469

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### Clinical Limitations of Perfusion Imaging

Lack of Standardisation

Kane et al (2007), Stroke

Contrast Toxicity

Nephrogenic Systemic Fibrosis  
Cowper et al (2008) *J Am Coll Radiol*

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### Oxygen and the Penumbra

Cerebral perfusion pressure (CPP)  
Cerebral blood flow (CBF)  
Cerebral blood volume (CBV)  
Oxygen extraction fraction (OEF)

DWI      PWI      BOLD      Final Infarction

Siemonsen (2008), Radiology

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### Assessment of static T2\*-weighted signal intensities

Patient 1      Patient 2

OEF      T2\*

Donawijk (2009) *Cerebrovascular Diseases*

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### Oxygen as a Contrast Agent?

*Magnetic Resonance in Medicine* 49:271-277 (2003)

**Oxygen-Enhanced MRI of the Brain**  
Christoph Losert,\* Michael Peiler, Philipp Schneider, and Maximilian Reiser

*Journal of Magnetic Resonance Imaging* 20:1000-1008 (2004)

**Inhaled Oxygen: A Brain MR Contrast Agent?**  
Yves Derbaix, Philippe Trounev, Francis Turjman, Roger Y. Kwiat, Estelita Falles, and Jean Claude Formisano

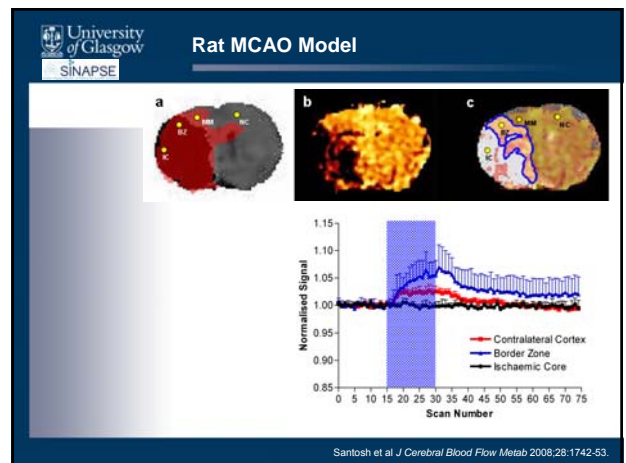
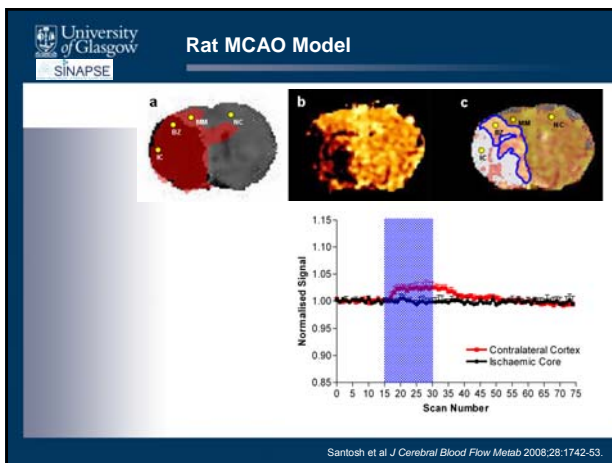
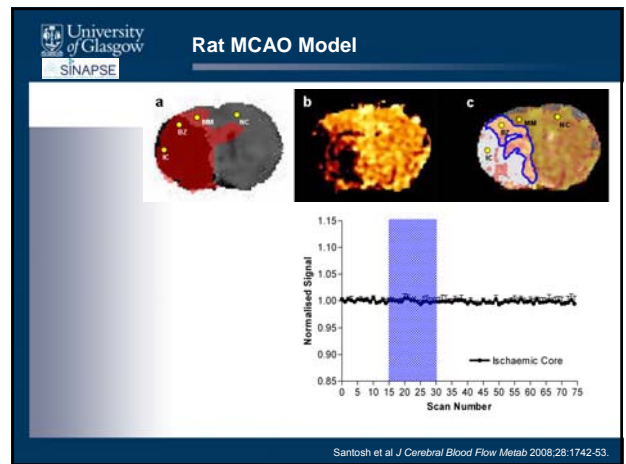
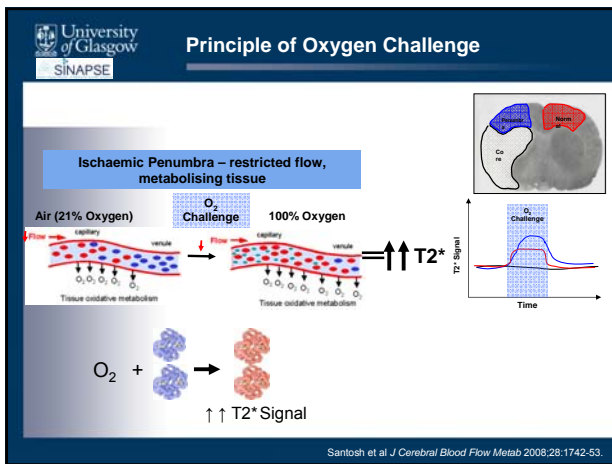
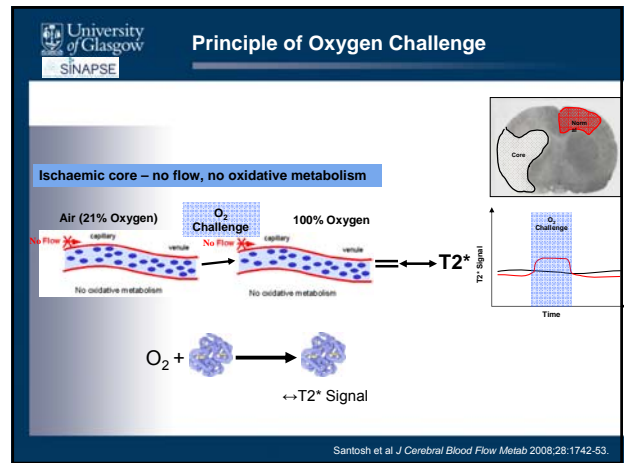
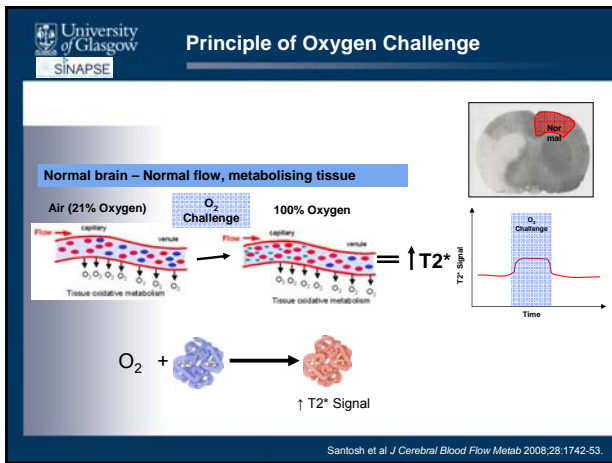
*Journal of Magnetic Resonance Imaging* 20:1000-1008 (2004)

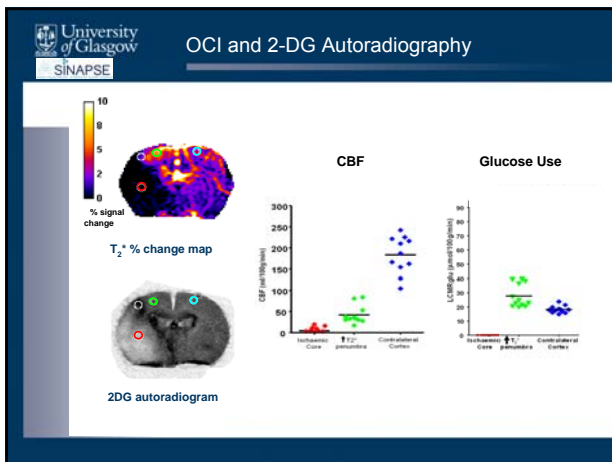
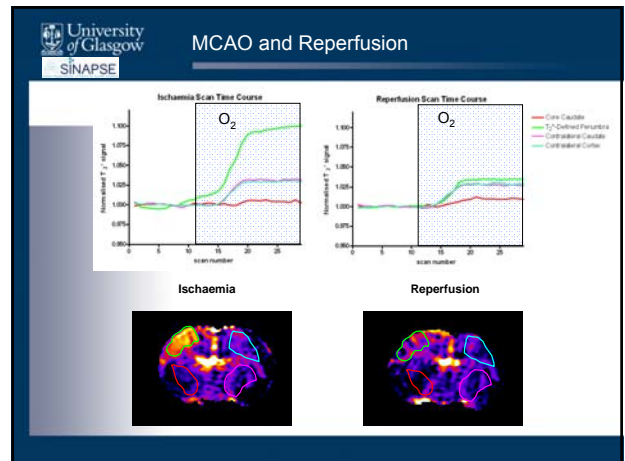
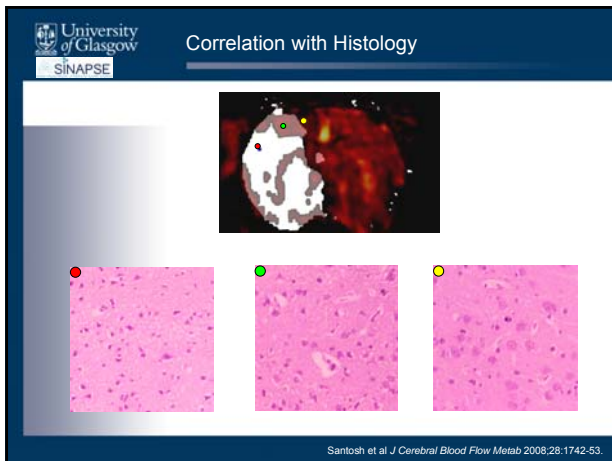
**Measurement of Cerebral Blood Volume in Humans Using Hyperoxic MRI Contrast**  
Daniel Bulte, PhD,\* Peter Chiarelli, DPhil, Richard Wise, PhD, and Peter Jezzard, PhD

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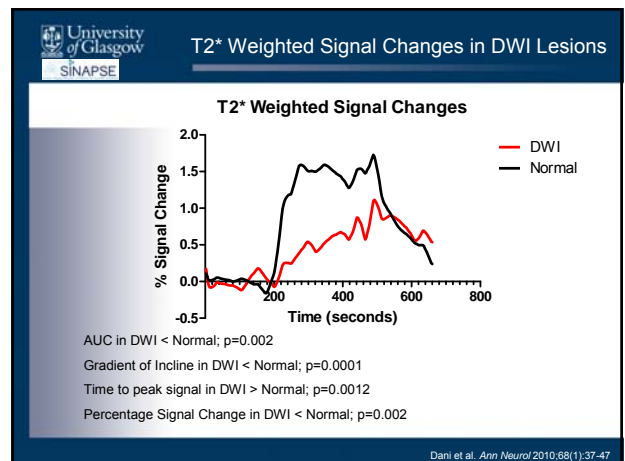
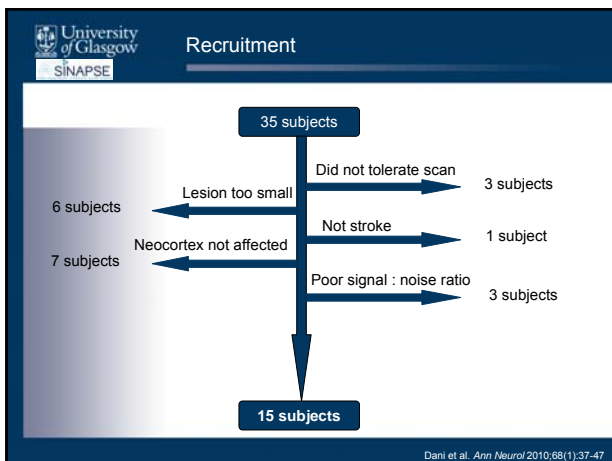
### Bench to Bedside to Bench Approach – A Translational Cycle

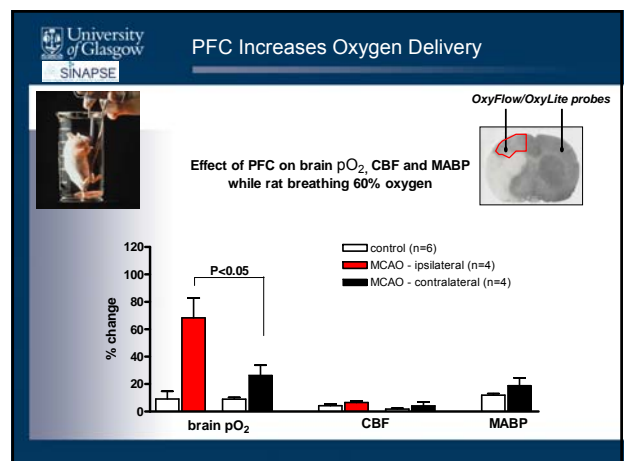
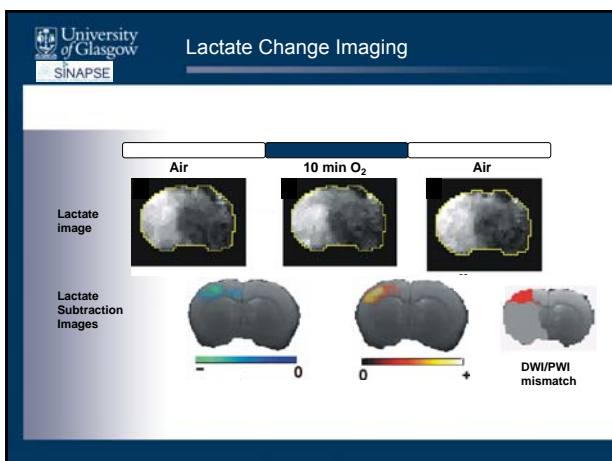
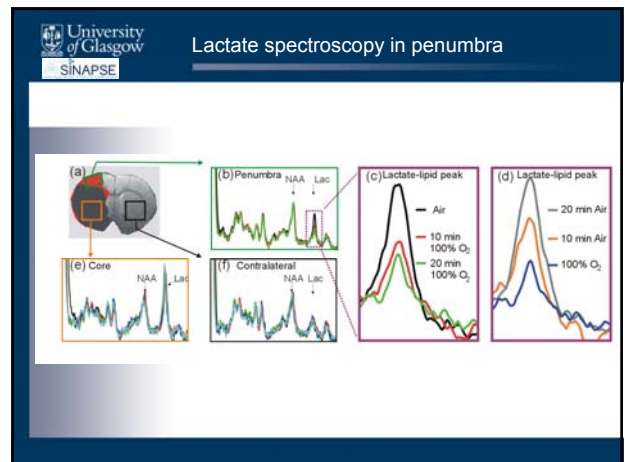
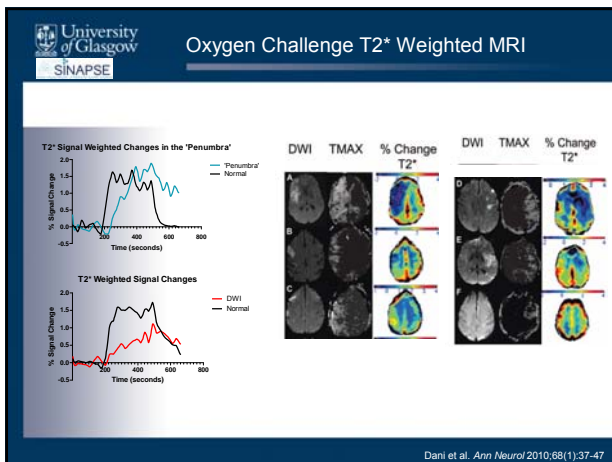
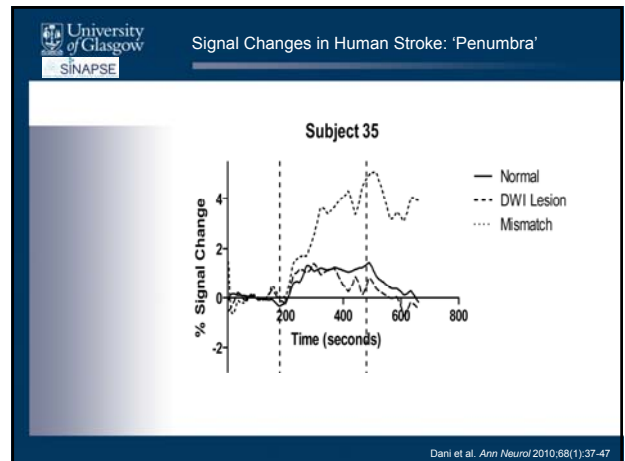
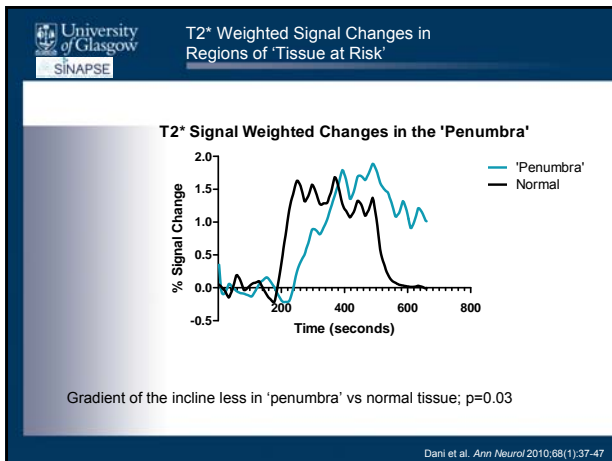
The diagram illustrates a circular translational cycle. At the top is a bench setting with an MRI scanner. An arrow points to a patient in a hospital bed. Another arrow points to a mouse. A final arrow points back to the bench setting, completing the cycle.

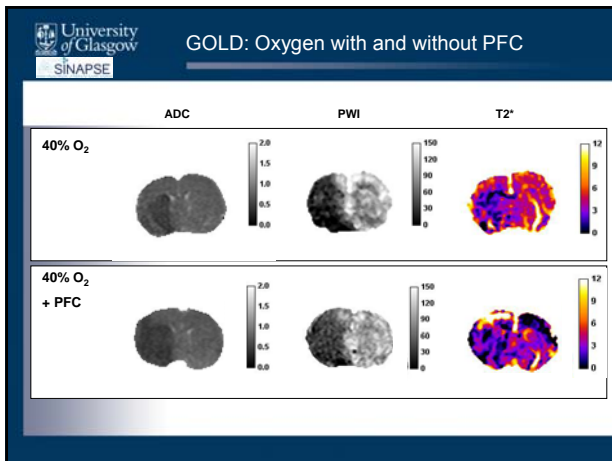




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- ### Human Translation
- 35 subjects
  - Age; mean 70yrs, range 61-95yrs
  - 23 male (66%)
  - Median NIHSS = 12, IQR 5-20
  - Median time to imaging 18.0h (IQR 6.5-23h)
  - 13 subjects <9h
  - 18 pts received r-tPA
- Dani et al. *Ann Neurol* 2010;68(1):37-47







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- ### Summary
- Current imaging for stroke has limitations
  - Physiological imaging promises possible extension of reperfusion therapy to a wider population
  - Oxygen Challenge Imaging is clinically feasible and identifies tissue with characteristics of penumbra
  - Addition of lactate imaging and PFC-enhanced GOLD imaging in combination promise more rigorous penumbral diagnosis

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	Neurosciences Foundation	Celestine Santosh
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	<b>GEMRIC</b>	<b>Neurology</b>
	I Mhairi Macrae	Krishna Dani
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