



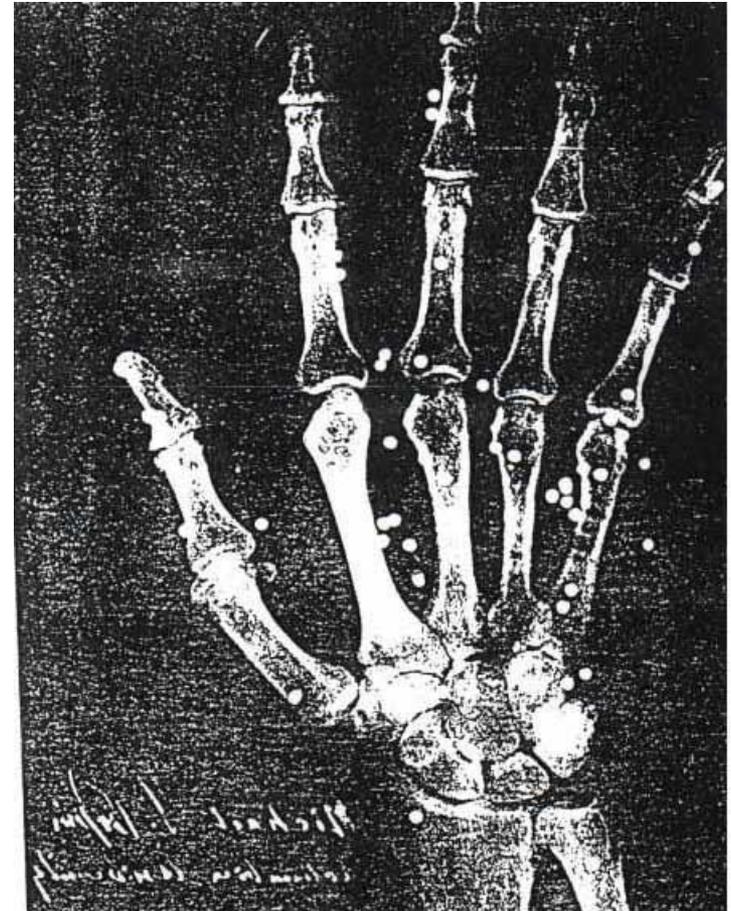
PHARMACEUTICAL COMPANIES OF *Johnson & Johnson*

How *in vivo* Imaging at MICA Will Help Janssen in Developing New Medical Treatments

In Vivo Imaging and the Foundation of Modern Medicine



November 1895:
Discovery of the X-Ray by Wilhelm Röntgen



January 1896:
First medical X-Ray in the US by Michael Pupin

In Vivo Imaging and Clinical Medicine

In vivo imaging is used for:

- Diagnosis
- Deciding on a treatment
- Determining whether a treatment is effective

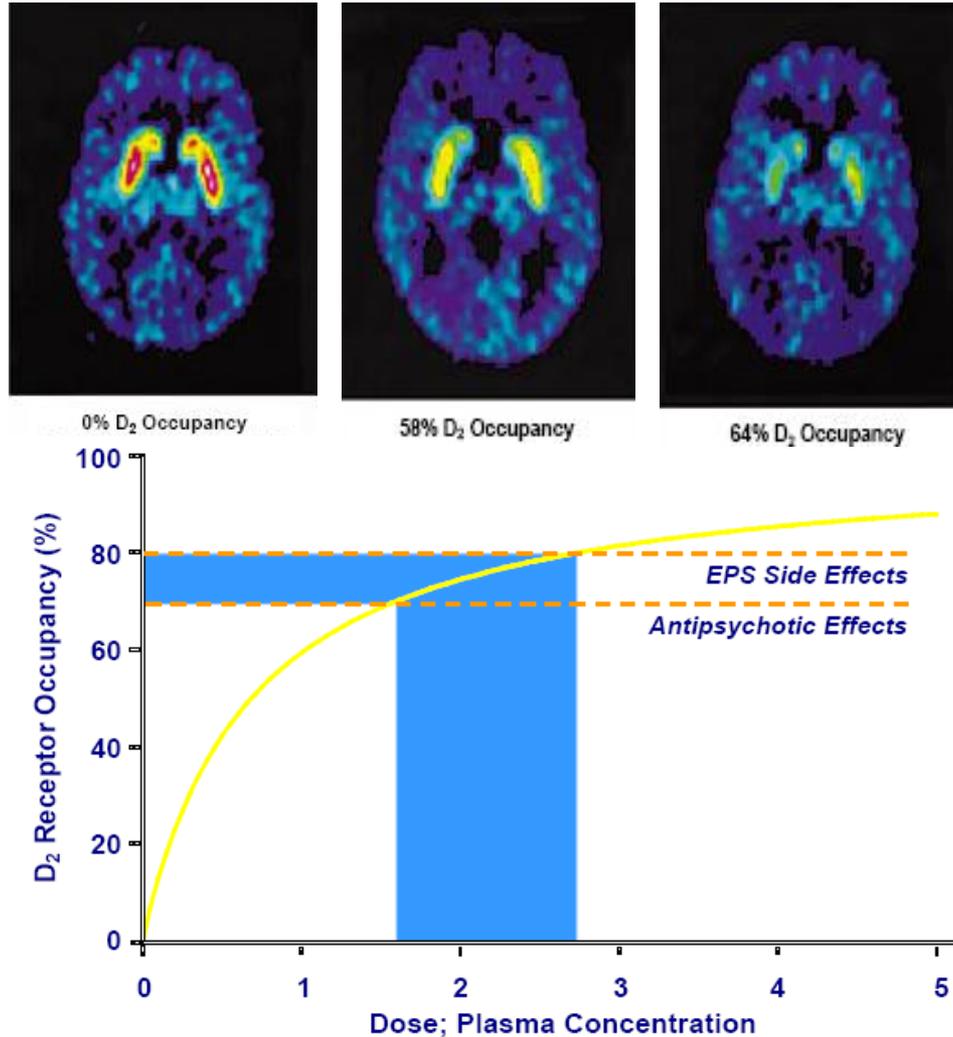
In vivo imaging allows us to see $\left(\begin{array}{c} \underline{\text{what}} \\ \underline{\text{where}} \\ \underline{\text{when}} \end{array} \right)$ something is occurring

In vivo imaging creates information that can be readily shared and easily understood

In Vivo Imaging and Clinical Drug Development

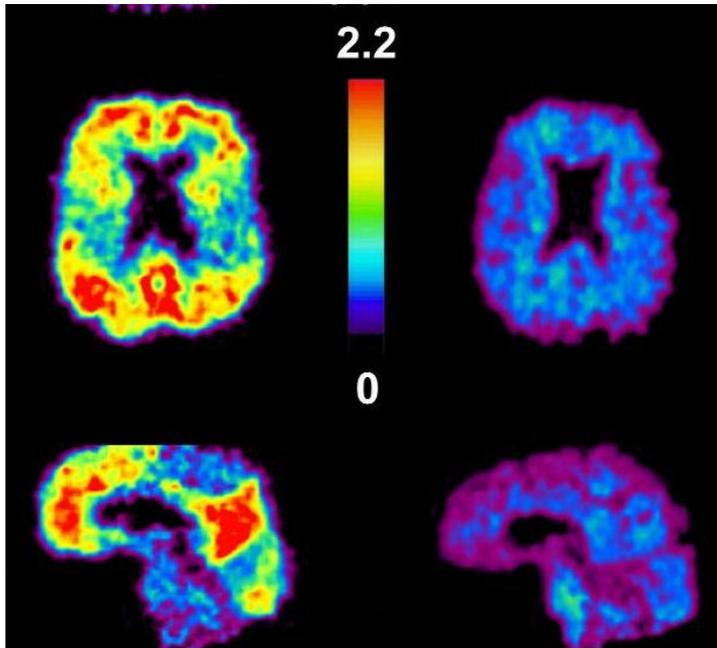
- **Pharmacology: where is my drug and what is it doing?**
 - Radioligand labeling is most often needed for signal detection and PET is used most often because it is the most quantitative method available
 - Examples are ‘occupancy’ studies, in vivo tissue distribution studies of a clinical lead, and measuring a ‘downstream’ effect of a drug on a molecular target
- **Disease: am I treating the right patient, and what is my drug doing to the disease?**
 - Best examples are stroke and MS for CNS drugs
 - Alzheimer’s disease and Parkinson’s disease are emerging
 - ‘Structural’ MRI often used: widely available in clinic, superior anatomical resolution of the brain
 - PET/SPECT are emerging as diagnostics and for staging of disease
- **Behavioral systems: am I doing something that matters, and should I be looking for new drugs?**
 - Emerging technology based on functional imaging (e.g., MRI, FDG, E.E.G.) for identifying critical behavioral ‘networks’ (e.g., fear response, perceptual cognition)

PET Receptor Imaging for Determining the Amount of a New Drug to be Used for Testing in Patients with Schizophrenia



PET Amyloid Imaging as Means of Showing Treatment Effect in Alzheimer's Disease

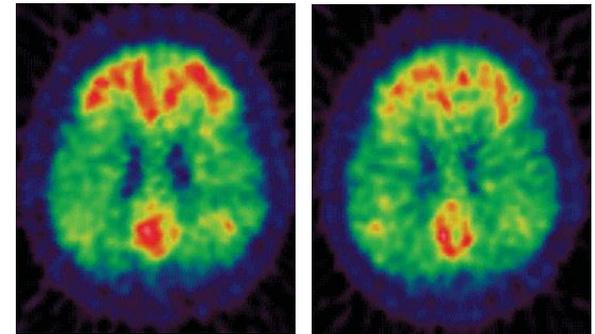
PET Images with the beta amyloid targeting probe: ^{11}C -PiB



Patient with AD

Healthy elderly control

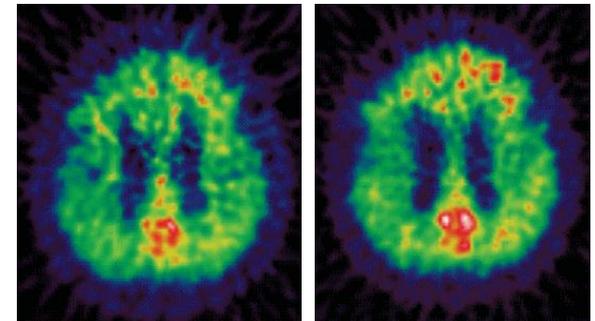
Patient with AD treated with bapineuzumab



Before treatment

After 78 weeks treatment

Patient with AD treated with placebo



Why Preclinical Imaging?

- Preclinical experiments allow for rapid and intensive measurements to evaluate the potential safety and efficacy of new treatments
- Preclinical imaging methods can be highly predictive of the behavior of new treatments in humans
 - Measuring where a new treatment goes in the body
 - Determining whether a new treatment will get into the brain
 - Determining whether enough of the new treatment gets to the disease target
 - Determining the most reliable measurement method for new imaging probes
- Allows for exploring the possible effects on disease
 - Disease models, such as transgenic mouse strains, allow for testing whether a new treatment is having an effect on pathological features
- Ability to measure change in the brain over short periods of time
 - Preclinical models can be used to evaluate development, interruptions to development, and disease effects in weeks to months rather than many years

Imaging Needs to be Incorporated Early in Treatment Discovery and Development

~ 2 - 3 Years

- **Target Identification and Validation:**
 - Imaging included as an element for review and possible action in the project plan
- **‘Hit to lead’:** initiation of the imaging plan
 - Drug effects on target known?
 - Drug effects on pathway known?
 - Target specific ligand
 - Target: density and distribution? Library: suitable physical chemistry and pharmacology?
 - Initiate radiotracer lead development
- **Lead Optimization:** feasibility and scope of the imaging plan
 - Radioligand lead optimization
 - Pharmacodynamic effect: preclinical testing possible?
 - Effect compartment exposure in clinic anticipated to be a problem?
 - Evidence of an effect on relevant preclinical disease or behavioral model?
- **New Molecule/Biologic declaration:** qualification of the imaging plan
 - Radioligand lead selection
 - Validation and development of new probes for clinical use
 - Translation of other preclinical imaging methods to clinical imaging
- **Proof of Concept:** clinical implementation of the imaging plan
 - pharmacodynamic effect, target validation, tissue exposure and/or target exposure

Performance Characteristics of Clinical Imaging Methods

| Imaging Method | Temporal resolution | Spatial resolution | Sensitivity | Energy $\Delta E=h\nu$ |
|----------------|-----------------------------------------------|--------------------------------------------|-------------------------|------------------------|
| MEG | 1 msec | 5 mm | | |
| EEG | 1 msec | 10–15 mm | | |
| MRI | 100 msec single slice 3 sec multiple slice | 3.5 mm [†] 1-2 mm [‡] | 10 ⁻⁵ molar | 10 ⁷ Hz |
| PET | 45 sec* 20 min** | 6.5 mm* 4 mm** | 10 ⁻¹² molar | 10 ¹⁷ Hz |
| SPECT | >60 sec | 6–8 mm | 10 ⁻¹² molar | 10 ¹⁷ Hz |

† GE BOLD 1.5T

* H₂¹⁵O to measure CBF

‡ SE-BOLD 7T

**¹⁸FDG to measure CMRglu

Adapted from: Farde, Rosen, Volkow PNAS 1997

Logothetis Nature 2008

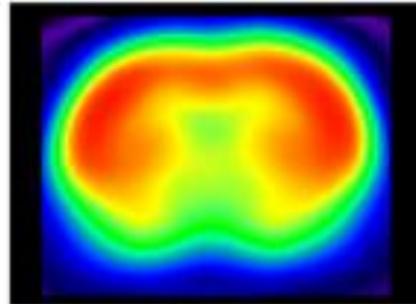
PET Imaging in CNS Drug Development

- **The sensitivity of the method allows:**
 - Measurement and distribution of drug targets in vivo
 - Measurement of drug compound in the target tissue in vivo
 - Measurement of metabolic processes in vivo
- **Multiple isotopes allows:**
 - Range of time courses for measurement
 - Flexibility in labeling small molecules and biologics
- **Readily translated from preclinical models to clinical application**
 - Serial assessments are possible: humans and preclinical species can serve as their own controls
- **An accessible technology for clinical trials:**
 - Hospital based
 - Increasing availability through adoption of PET for diagnosis and treatment
 - Increasing number of ^{18}F labeled tracers

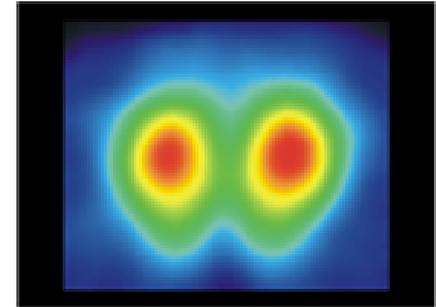
MRI Imaging in CNS Drug Development

- **The sensitivity of the method allows:**
 - High resolution definition of tissue anatomy and tissue types
 - Correlation of tissue changes and clinical disease state
- **Multiple sequences allow:**
 - Ability to assess functional changes and connections in the brain
 - Ability to assess subtle changes in different tissue types
- **Readily translated from preclinical models to clinical application**
 - Serial assessments are possible: humans and preclinical species can serve as their own controls
 - Potential for assessing effects over shorter time epochs in preclinical models
- **An accessible technology for clinical trials:**
 - Hospital based
 - Adaptable for wide range of patient studies
 - Increasing availability of new and possibly more sensitive techniques
- **Data can be integrated across multiple sites**
 - Harmonization of acquisition, processing, and analyses

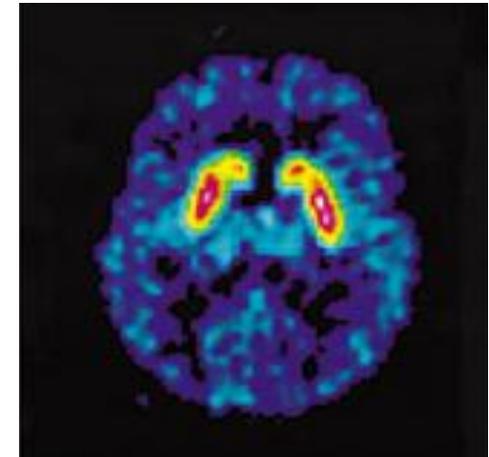
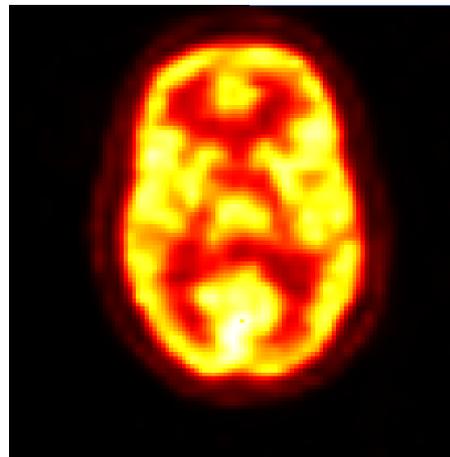
Preclinical Imaging Can Employ and Test the Same Methods Used in Clinical Studies



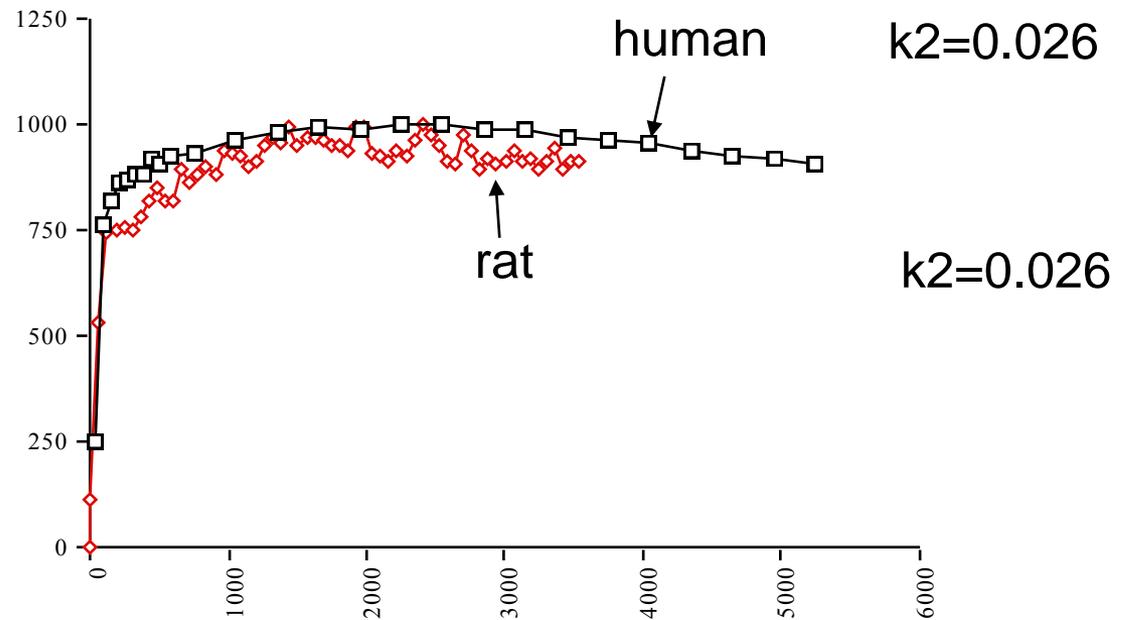
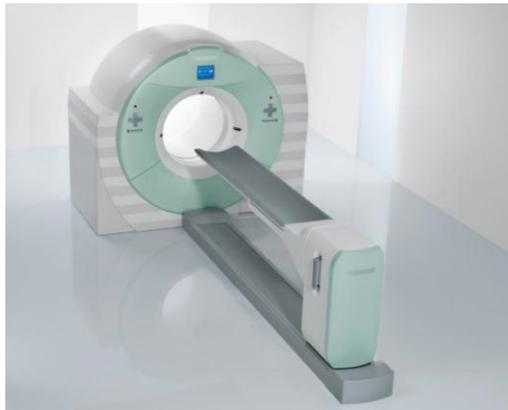
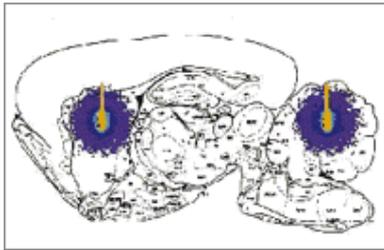
^{18}F -FDG



^{11}C -raclopride



Preclinical Methods Can be Highly Predictive of the Performance of New Imaging Probes in Human Imaging



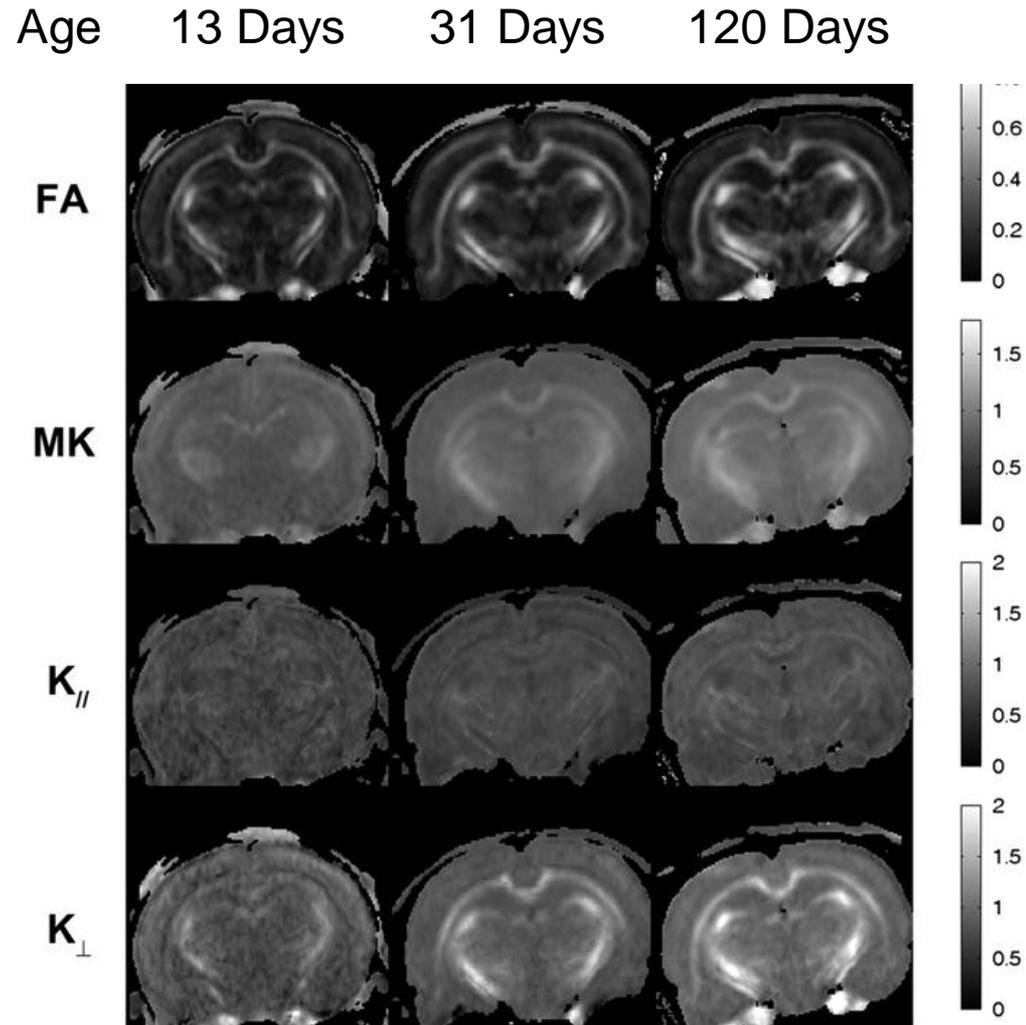
Preclinical MRI May Allow for Discovery of Sensitive Methods of Seeing Changes in Brain

•This is an MRI study of brain maturation in rat. The top row shows the signal using diffusion tensor imaging, the lower rows are parameters measured using diffusion kurtosis imaging.

•FA (fractional anisotropy) is from diffusion tensor imaging (DTI)

•MK, $K_{//}$, and K_{\perp} are from diffusion kurtosis imaging (DKI: with mean, axial, and radial values).

•DKI is an emerging method that could provide a complementary method for detection and measuring progression of disease.



Janssen Goals for MICA

- Find the best preclinical imaging methods for identifying new treatments of disease through collaboration
 - Use of *in vivo* imaging to help identify the pharmacological effects of new treatments
 - Use of *in vivo* imaging to help identify biomarkers of the earliest stages of disease and progression
- Establishing the best methods for acquiring imaging data and their analysis
- Achieve this through active and vigorous collaboration with UA and UZA
- Through these efforts, to develop treatments that can transform the lives of patients with devastating illnesses

Acknowledgements

Janssen

- Paul Acton
- Kim Cryns
- Stefanie Dedeurwaerdere
- Shelly Geers
- Stef Heylen
- Tom Heyman
- Eric Karran
- Xavier Langlois
- Ludo Lauwers
- Hussein Manji
- Vic Maes
- Theo Meert
- Henk Sipma
- Thomas Steckler
- Paul Stoffels
- Roy Twyman
- Cathy Van den Eynde
- Luc Van Nueten
- Christophe Verbruggen

UA/UZA

- Ingrid Cornille
- Martin Decancq
- Steven Deleye
- Bart Heynen
- Christel Jacobs
- Philippe Jorens
- Elke Smits
- Steven Staelens
- Sigrid Stroobants
- Jean-Pierre Timmermans
- Dominique Vanderghinste
- Annemie Van Der Linden
- Johnny Van der Straeten
- Tine Wyckhuys,
- Leonie Wyffels