Simultaneous ^{18}F-FDG PET/MR imaging for metastasis identification in a disseminated human preclinical melanoma model

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Introduction

- **Melanoma** = skin cancer with high risk of metastatic progression.
  ➔ metastases associated with poor prognosis.
- **Rat strain**
  - *Nude* rat from Charles River (NIH-*Foxn1^{rnu}*)
  - SDRG model from GenOway* (Rag1$^{-/-}$ Il2rγ$^{-/-}$)
- **Imaging** is an essential tool:
  - to assess tumor stage
  - to monitor disease progression
  - to evaluate therapy response
- **A single imaging technique cannot efficiently detect all metastases:**
  - ^{18}F-FDG PET background signal (brain, kidneys, heart)
  - MRI motion artifacts (cardiorespiratory system, digestive tract peristalsis)

OBJECTIVES:

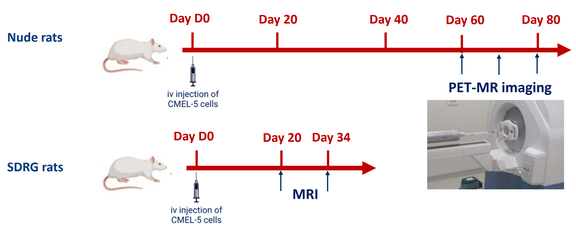
1. To evaluate the metastatic development of human melanoma (CMEL-5) in two rat strains (*Nude* and SDRG rats)

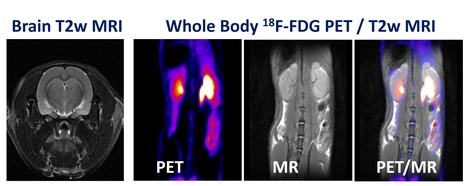
2. To evaluate the complementarity of PET and MR to detect metastases in a disseminated melanoma model

Methods

- On Day 0**, Female *Nude* and SRDG rats** were intravenously injected with **CMEL-5 cells**. The CMEL-5 human melanoma cell line originates from a brain metastasis induced by intravenous injection of LB1319-MEL cells (est. from metastatic malignant melanoma) in *Nude* mice.
- ***Nude* rats** were imaged on days 60, 70, and 80 post-injection, using **brain T2-weighted (T2w) MRI and whole-body simultaneous ^{18}F-FDG (10-15 MBq) PET/MR.** Images were acquired in a preclinical system consisting of a 10-cm axial field of view SiPM PET detector fully integrated in a 7T dry magnet (MR Solutions Ltd, Guildford, UK).
- **SDRG rats** were imaged on days 20 and 34 post-injection using **brain and whole-body T2-weighted (T2w) MRI only.** Images were acquired in a preclinical 4.7T MRI (Pharmascan, Bruker).
- Visual detection and quantitative analysis of lesions were performed on MRI or PET/MR images, and results were confronted with necropsy (melanin pigmented lesions) and gamma counting data.

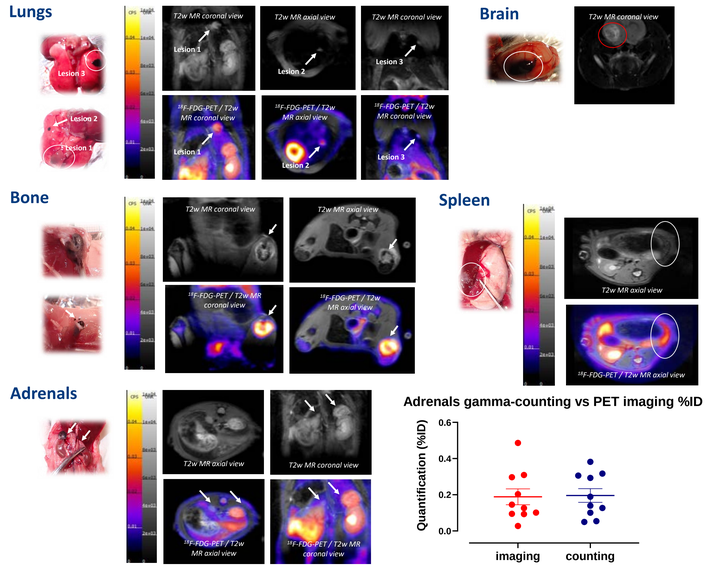
All animal procedures were approved by the Animal Care and Use Committee of Oncodesign Services (Oncomet - CNREEA agreement N° 91).





Results

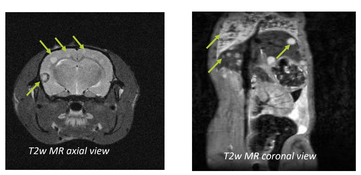
1. *Nude* rats



- From day 60 after CMEL-5 cell injection, **all animals exhibited metastases** in one to four different locations.
- PET quantification in adrenals (weights ranging from 69 to 368 mg) was consistent with gamma counting results.
- **MRI further allowed precise contouring** of each organ of interest to effectively identify bone, lung, adrenal and spleen metastases with enhanced ^{18}F-FDG uptake.
- Most of **metastases locations found in clinical setting were detected** in our model by simultaneous ^{18}F-FDG PET/MR imaging.
- **Small lesions** below PET spatial resolution limit (i.e. <1 mm) were **not detected by imaging.**
- Body weight monitoring showed regular weight gain throughout the 80 days duration of the study. The clinical follow-up of the animals **showed no significant predictive signs of metastatic development** (until the euthanasia).

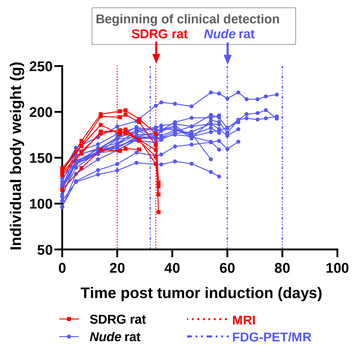
2. SDRG rats

- On day 20 post-CMEL-5 cell injection, **no metastases were detected** by MRI.
- On day 34 post-CMEL-5 cell injection, **all animals exhibited metastases** in one to three different locations (i.e. brain, liver and lungs).
- Body weight monitoring showed steady weight gain up to 28 days post cell injection. Afterwards, **rapid weight loss was a significant predictor of metastatic development**



3. Clinical observations *Nude* rats vs. SDRG Rats

Body weight monitoring



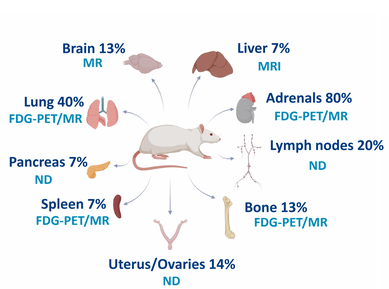
Lesion identification at necropsy

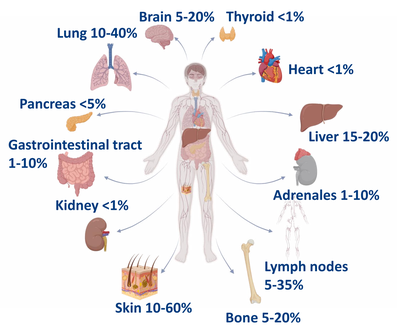
Organs/Tissues	*Nude* Rats (D60 to D80)	SDRG Rats (D34)
Brain	+	+++
Lungs	++	+++
Pancreas	+	+
Liver	+	+
Spleen	+	+
Adrenals	+++	+
Lymph node	++	+
Bone	+	+

- Compared to *Nude* rats, SDRG rats showed a rapid body weight loss. The observed body weight loss is highly associated with metastatic development in SDRG rats.
- SDRG rats showed rapid dissemination of metastases mainly in the brain and lungs. The propagation of metastases in *Nude* rats is longer and the spread is **less specific**.

Conclusion

- The two experimental models of disseminated CMEL-5 melanoma in *Nude* and SDRG rats mimic the human pathology. Both models appear to be **promising tools to monitor therapy response** and potentially recognize progression from pseudo-progression.
- The SDRG strain is more permissive than the *Nude* strain and shows **faster metastatic development, especially in the brain, lungs and liver**.
- **Simultaneous PET/MR imaging has shown to be more effective than stand-alone techniques in detecting melanoma dissemination,** except for brain and small lesions for which the PET data are altered by partial volume effect.





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