“PET Molecular Imaging in oncology: drug development or (and?) routine clinical usage”

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Introduction

- Biotech funded by Syncona Partners, based Oxford Science Park
- Licensing of IP from GE Healthcare
- Mission: To develop and commercialize Fluciclovine [18F], aka FACBC, a PET amino acid imaging agent for the detection of recurrent prostate cancer and glioma
- Experienced management team - medical imaging / drug development.
In this presentation

• Review rationale for amino acid PET imaging in cancer and some of the radiolabelled amino acids that have been developed

• Discuss challenges for transition of molecular imaging from ‘scientifically interesting’ to ‘clinically & commercially useful’

• Review unmet imaging needs in prostate cancer clinical decision making and the ongoing development of new tracers for PSA recurrent prostate cancer

Disclaimer: For educational purposes only. Some of the products discussed are still under development and may never come to market.
Scientific basis for amino acid PET imaging in oncology

- Cancer cells are rapidly proliferating and may have aberrant cell energetics. Amino acids are in demand for both anabolism & catabolism.

- Mammalian cells may have many aa transporters, four of which in particular are over-expressed in cancer cells: ASCT2; LAT1; xCT and ATB^{0,+} (1).

- Certain amino acids (leucine, glutamine) are involved in pro-oncogenic signaling via mTOR, activity in prostate cancer cells is linked to androgen driven LAT1 & LAT3 expression (2).

- Amino acid metabolism as a drug target is not new, with drugs such as asparaginase used in acute lymphoblastic leukaemia and LAT1 transporting the anti-cancer drug melphalan (3). More recently glutaminase inhibition has also been shown to be a viable drug target (4).

Radiolabelled amino acids (5)

- F-DOPA used in neuroendocrine tumors and Parkinson’s disease; $[^{18}\text{F}]$ FET and $[^{11}\text{C}]$ MET in glioma; fluciclovine transported by ASCT2 & LAT1 (6) but not metabolised or incorporated into protein.

Challenges to wider use of new PET tracers in oncology

- Most PET agents used in drug development are available at few centres (mostly neuro)
- A (very) limited number are widely available for diagnostic use, even fewer with NDA/MAA
- CT/MR/SPECT and FDG have shown widespread utility in oncology applications, with some exceptions
- So...how do we go from beautiful science to commercial use for new tracers?
- Find an initial ‘killer app’ for product
  - high un-met need
  - clear therapy ‘decision node’
  - willingness to pay
The ‘niche’ of biochemically recurrent prostate cancer

Clinicians identify 5 areas for better imaging:

1. Biopsy guidance after repeat negative TRUS biopsy
2. Staging high risk primary cases for LN or bone involvement
3. 1° radiotherapy planning
4. Detection of local vs distant PSA recurrence (BCR)
5. Monitoring of progression or response in late stage disease

In BCR choice made between focal curative or systemic therapy

Only 10-20% BCR patients in the USA have positive findings with conventional imaging (7)

Non FDG PET tracers in BCR Pca

- Several recent reviews, see below (8,9,10,11).

- **Choline & acetate.** Meta-analyses: $^{11}$C Cho more sensitive than $^{18}$F Cho in $^{1}$o LN staging (9); $^{18}$F cho more sens. in BCR, inc. LR & bone (10); CHO higher sens vs $^{99m}$Tc BS (11). $^{11}$C Ac, small intra-pt study seems similar to Cho (12).

- $^{18}$F NaF intra-pt study shows higher sensitivity vs $^{18}$F-Cho for spinal mets, however with much lower specificity (13).

- **Fluciclovine $^{18}$F:** In 28 pts with negative conventional imaging, (mean PSA 2.9) $^{11}$C Cho visualised 7 lesions / 5 pts, fluciclovine detected 18 lesions in 10 patients (14).

- Many PSMA (PET/SPECT: $^{99m}$Tc, $^{18}$F, $^{68}$Ga, $^{89}$Zr) industrial effort aligned with stratifying PSMA therapy. In a 37 pt study (avg PSA 11.1) total of 78 lesions in 32 pts were detected with $^{68}$Ga-PSMA PET/CT & 56 in 26 patients using Choline PET/CT (15). Impact of PSMA heterogeneity (16) on diagnostic utility is not established.

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CONCLUSION

Newer PET molecular imaging agents have the potential to solve key diagnostic challenges in oncology applications where anatomic imaging and FDG perform poorly.

Widespread availability of novel PET agents for diagnostic use will enhance access for drug development researchers wishing to investigate new mechanisms of action, such as those associated with amino acid metabolism or specific receptor based imaging.

THANK YOU