

1  **Molecular Imaging Program**

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2  **Objectives**

- Non-invasive functional imaging as a powerful tool
  - SPECT and PET/CT
- Novel radiotracers and malignancies
- Clinical trials

3  **TRACERS CHELATED TO DRUGS**

4  **In-111 Trastuzumab Study**

- In-111 CHX-A" DTPA trastuzumab
  - Noninvasive assessment of HER2/Neu expression
- HER2
  - membrane-bound receptor stimulating cell growth
- Over-expression portends poor prognosis
  - breast, ovarian, pancreatic adeno, colorectal, gastric, uterine cervical, prostate and lung adeno cancers
- Trastuzumab (Herceptin)
  - Useful tx in overexpressing HER2/Neu breast cancers
  - Human biodistribution not well characterized
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6  **Objectives**

- Identify HER2/Neu expressing mets
- Monitor tx response
- Evaluate human biodistribution
  - Establish dosimetry for future radioimmunotx
- Eligibility
  - Primary or metastatic CA with solid tumor  $\geq 1.5$  cm
    - not melanoma, basal cell, sarcoma or lymphoma
  - HER2/Neu expression status by IHC or FISH
    - Or willing to have tumor bx for IHC
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7  **Study Design**

- Goal of 20 patients
- 4 imaging scans

8  **<sup>111</sup>In DTPA Trastuzumab in Breast Cancer**9  **F18-FPAC**

- Paclitaxel - chemo agent
  - Tumor resistance develops due to lack of sufficient accumulation
- <sup>18</sup>F FPAC- paclitaxel radiotracer
  - Biodistribution similar to paclitaxel
  - Could help select pts likely to respond to tx
  - Substrate of Pgp
    - Membrane pump overexpression related to multidrug resistance
    - Can serve as surrogate for Pgp fxn in tumors/nl tissue

10  **Pgp Pump**11 

- Objective
  - Determine if FPAC uptake in tumors is different than uptake in normal background tissues
  - Determine safety of FPAC
- Secondary objectives
  - Compare FPAC uptake with FDG uptake in solid tumors
  - Make preliminary comparisons of FPAC uptake with treatment response and drug transporter expression when available
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- Eligibility
  - Breast, adrenal, renal or lung Ca with  $\geq 1$  cm lesion above the diaphragm
    - Physiologic excretion will obscure other lesions
  - No other investigational agent 24hrs before or after FPAC injection
- 2 arms: 15 patients each
  - Tumors historically sensitive to paclitaxel
    - Lung and breast
  - Tumors not usually responsive to paclitaxel (negative controls)
    - Adrenal and renal

13  **Study Design**14  **Normal biodistribution of <sup>18</sup>F FPAC**

- At 1, 2 and 3 hrs post injection
- Physiologic excretion through biliary and bowel

15  **FDG and FPAC in breast tumor**

A: FDG PET/CT- uptake in primary tumor (arrow), mediastinum and hila

B: CT

C: FPAC PET/CT- uptake in primary tumor (dotted arrow) and myocardium (arrow)

D: FDG PET/CT- mid therapy scan (3mos) with resolution in primary tumor and partial

resolution in mediastinum and hila

16  **In111 Amatuximab (MORab-009)**

- MORab: monoclonal IgG ab against human mesothelin
- Mesothelin: glycosyl-phosphatidyl inositol membrane glycoprotein
  - Cell adhesion and tumor metastasis
  - Over-expressed in many cancers
    - Pancreatic adenoCa, mesothelioma, ovarian epithelial, lung adeno, endometrial adenoCa, SCC of esophagus, lung, cervix

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- Objective
  - Determine biodistribution of In111 MORab in tumor and nontumor tissues
- Eligibility
  - Mesothelin-expressing cancer
    - Pancreatic adenoCa, mesothelioma, mesothelin+ ovarian Ca, NSCLC
  - Tumor not in liver  $\geq 1.5$ cm
  - No prior tx with MORab
  - No immunomodulatory tx within 3 mos
    - Interferons, Ig tx, Interleukin 1 receptor antagonist, systemic corticosteroids

18  **Study Design**

19  **<sup>18</sup>F FdCyd Imaging**

- DNA hypermethylation results in silencing of tumor suppressor genes
- 5-fluoro-2'-deoxycytidine (FdCyd) inhibits DNA methyltransferase (needed for DNA methylation)
  - Re-expression of tumor suppressor genes
- FdCyd with tetrahydrouridine (THU) has shown superior anti-tumor activity
  - Response can be variable in some
- <sup>18</sup>F FdCyd is chemically identical to drug
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- Objectives
  - Determine safety of <sup>18</sup>F FdCyd with THU
  - Observe biodistribution and radiation dosimetry
- Eligibility
  - Pts on NCI Phase II study evaluating FdCyd with THU
    - Non-small cell lung ca, head/neck ca, breast ca, urothelial transitional cell ca
  - Target lesion  $\geq 10$ mm
- Accrual Goal: 15 patients

22  **Study Design**

23  **Imaging Sessions**

- 24  **<sup>90</sup>Y Daclizumab Radioimmunotherapy in Hodgkin's Lymphoma**
- Single institution non-randomized phase I/II
  - <sup>90</sup>Y daclizumab RIT in relapsed or refractory HL
    - High-dose BEAM
      - Carmustine, etoposide, cytarabine, melphalan
    - autologous hematopoietic stem cell transplant (ASCT)
  - Hodgkin's Lymphoma
    - 30-65% achieve long-term disease free survival in relapsed patients on high dose chemo and ASCT
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- <sup>90</sup>Y daclizumab
    - Humanized IgG1 monoclonal ab targeting CD25
      - High affinity interleukin-2 receptor (IL-2Ra)
      - Often in Reed-Sternberg cells and T cell infiltrates of HL
    - Yttrium-90: beta-emitting isotope
      - targeted radiation therapy to tumor
  - 63% response rate in 30 patients with CD25 relapsed/refractory HL

26  **<sup>90</sup>Y Labeled Antibody**

27  **Crossfire Effect of <sup>90</sup>Y antibody**

28  **Objectives**

- Phase I
  - Assess safety and adverse events with <sup>90</sup>Y
  - Determine maximum tolerated dose
- Phase II
  - Assess frequency of failure to engraft, MDS, secondary leukemia, abn bone-marrow markers
  - Estimate response rate (complete and partial)
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29  **Eligibility**

- Relapsed or refractory HL
  - 10% CD25 expression on malignant cells
  - Lesion at least 1cm
  - Not lymphocyte predominant
  - No pre-existing MDS or marrow abn
  - No chemo or other systemic HL tx for 4 weeks prior to trial entry
  - No prior autologous or allogeneic SCT
- Dose escalation design
  - Phase I: max of 42 pts
  - Phase II: max of 45 pts
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30  **Study Design**

- Indium-111-daclizumab (5 mCi) imaging will be performed concurrently with each <sup>90</sup>Y-daclizumab RIT and at day 100 after ASCT.

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31  **Complete response to <sup>90</sup>Y-daclizumab**32  **TRACERS AS SUBSTRATE ANALOGS**33  **<sup>18</sup>F FLT**

- Fluorothymidine is an analogue of thymidine
- Phosphorylated by thymidine kinase
  - Trapped in cell but not incorporated into DNA
- Thymidine kinase upregulated in DNA salvage pathway
  - Seen in actively dividing cells
- Enters cell through active transport and passive diffusion
- Indirect marker for cell proliferation

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34  **<sup>18</sup>F-FLT Lymphoma**

- Malignant lymphoma
  - 5<sup>th</sup> most frequent CA in US
  - Management depends on accurate staging and response to tx

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- <sup>18</sup>F FDG PET/CT
  - Useful in monitoring tx response (early and late) in lymphoma
  - Can distinguish between viable tumor and necrosis/fibrosis
  - Also seen in inflammation, apoptotic cells, granulomas, abscesses and sarcoidosis
- <sup>18</sup>F FLT
  - Associated with cell proliferation
  - Uptake in inflammatory lesions less prominent

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- Primary Objectives
  - <sup>18</sup>F FLT PET/CT as early indicator of response to tx in B and T cell lymphoma
  - <sup>18</sup>F FLT activity in residual masses post-tx
- Eligibility
  - Enrolled in lymphoma tx study at NIH or CALGB 50303
- 2 arms
  - Early response: treatment naïve or recurrent dz
  - Residual mass: FDG + mass  $\geq$  1cm

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- Accrual: 70 patients (40 early response/30 residual mass)
- 5 ml of venous blood obtained x 2
  - ~1 hour and ~2 hours post injection to correct the measured F-18 counts for the % metabolized F-18 FLT

39  **Lupron and <sup>18</sup>F FLT in allo-HSCT**

- Stem cell transplants are standard of care in ALL, AML and MDS
- Impaired lymphocyte reconstitution associated with morbidity and mortality after HSCT
- Lupron
  - GnRH analog
  - Enhances T and B lymphopoiesis through androgen withdrawal

40  **FLT Objectives**

- Predict marrow engraftment and immune reconstitution after allogeneic HSCT
- Demonstrate evidence of minimal residual disease at time of transplant
- Predict thymus recovery

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- Eligibility
  - >9 yrs and pubertal
  - >15yrs -40yrs
  - Requiring HSCT
    - AML, MDS with high risk cytogenetics, ALL
- Only patients receiving Lupron will undergo <sup>18</sup>F FLT imaging
  - 15 patients
  - Imaging day -1, 1 week, 4 weeks and later to assess for GVHD or immune recovery

42  **Study Design**43  **<sup>18</sup>F-FLT**44  **<sup>18</sup>F FLT- Neurofibromatosis**

- Neurofibromatosis Type 2 (NF2)
  - Predisposed to benign CNS/PNS tumors that can cause significant morbidity
    - Vestibular schwannomas, other schwannomas, meningiomas, gliomas, ependymomas
  - Natural history of NF2-associated tumor progression is unknown
    - Variable: not all tumors grow to cause neurologic sequelae

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- Objectives:
  - Determine if FDG and FLT uptake associated with growth rate of meningiomas and

Vs in NF2

- Future growth pattern prediction
- Eligibility:
  - NF2 with at least 3 intracranial tumors  $\geq$  1cm each
    - Must have 1 unoperated VS and 1 unoperated meningioma
    - No history of chemo or rad tx to brain
- Accrual goal: 12 patients

46  **Study Design**

47  **Meningiomas in NF2 Pt**

48  **Fluciclitide**

- Angiogenesis upregulated in many tumors
- [<sup>18</sup>F]AH-111585 (Fluciclitide)
  - Cyclic peptide containing RGD tripeptide
    - High affinity binding to  $\alpha_v\beta_3$  integrins
      - Expressed on proliferating endothelial cells associated with neovascularization in tumors and normal tissue
      - Also expressed on some tumor cell surfaces
  - May be useful angiogenesis marker for tumors

49  **Role of Integrins**

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51  **Fluciclitide in Breast Cancer**

52  **Fluciclitide-Surgery**

- Correlate Fluciclitide uptake and retention with  $\alpha_v\beta_3$  expression in tumors and other angiogenesis measures
  - Microvessel density (MVD) and biomarkers
  - Perfusion and tumor permeability through DCE-CT (optional)
- Eligibility
  - Primary or met tumors  $\geq$  2.5cm scheduled for resection or biopsy
    - High-grade glioma, lung ca (SC or NSC), H&N Ca, sarcoma, melanoma or RCC tumor  $\geq$  3cm
    - Target tumor not in liver
  - No anti-angiogenic agents within 60 days prior to PET (bevacizumab, sorafenib, sunitinib, etc)

53  **Study Design**

- Accrual goal: 30 patients

54  **F18- FACBC**

- <sup>18</sup>F FACBC (GE-148 (<sup>18</sup>F))
  - synthetic leucine amino acid analogue
    - Actively transported by amino acid transporters
  - Accumulates in cancer cells but not incorporated into proteins
    - Prostate Ca and malignant gliomas

- Low uptake in normal brain and urinary system

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- Objective
  - Differentiate uptake and retention of  $^{18}\text{F}$  FACBC in malignant prostate tumors, benign prostate pathology and normal prostate tissue
  - Assess safety of a single dose of  $^{18}\text{F}$  FACBC
- Eligibility
  - Prostate Cancer pt scheduled for prostatectomy at NIH

57  **Study Design**

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- MRI and PET/CT can be done on separate days
- Surgery must be complete within 3 weeks of PET/CT
- Accrual goal: 30 patients

58  **F18-FES and Z-endoxifen**

- 16 alpha- $^{18}\text{F}$ -fluoro-17 beta-estradiol (FES)
  - Analogue to estradiol: binds to estrogen receptor
    - Can evaluate estrogen receptor activity in certain tumors
- Z-endoxifen: oral rx
  - Active metabolite of tamoxifen
    - Bypasses possible hepatic enzyme polymorphisms
  - Binds to estrogen receptor and blocks estrogen
    - Inhibits tumor growth
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- Imaging Objective
  - Evaluate the change in  $^{18}\text{F}$  FES uptake on PET/CT in hormone receptor positive tumors before and after initiating treatment with oral Z-endoxifen
- Eligibility
  - ER+ or PR+ solid tumors (breast or other), desmoid tumors or gyn tumors
    - Breast: mets after chemo and hormone tx
    - Others: progression after standard tx

60  **Study Design**

- FES PET/CT optional
  - Baseline and repeated after 3<sup>rd</sup> dose of Z-endoxifen

- Dose escalation design: 3+3

61  **FES and ER+ Breast Cancer Mets**

62  **OTHERS**

63  **Ferumoxytol**

- Ferumoxytol
  - Semi-synthetic carbohydrate coated magnetic iron oxide preparation
    - Derivative of ferumoxtran-10
      - USPIO: ultrasmall superparamagnetic iron oxide particle
  - FDA approved for iron replacement tx
  - Taken up by normal lymph nodes, not by malignant nodes
  - Enhanced MRI with some efficacy at 24 hours
    - Benign nodes: drop in signal-to-noise ratio
    - Malignant nodes: no change

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- Objective
  - Determine optimal dose of Ferumoxytol for enhancing metastatic lymph nodes for prostate Ca
  - Determine safety of Ferumoxytol
- Eligibility
  - Prostate cancer pts scheduled to undergo prostatectomy
  - No evidence of iron overload on labs
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66  **Study Design**

- Accrual goal: 15 patients (5 per dose)

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68  **F18-NaF Prostate**

- F18 NaF- localizes in areas of bone turnover
  - High, rapid uptake with quick blood clearance
  - High quality images in less than 1 hour
  - PET/CT allows for quantitative analysis
- Metastatic prostate Ca
  - 80-90% involve axial skeleton
  - Primary cause of morbidity and mortality
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- Objectives
  - Evaluate feasibility of NaF PET/CT to quantitate bone mets in prostate cancer
    - Determine intra-pt reproducibility
- Eligibility

- Prostate adenoCa
- 2 arm design (30 patients each)
  - No known bone metastases
    - PSA  $\geq$  10 ng/mL or doubling time  $\leq$  6 months
  - Bone metastases
    - Any PSA level
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70  **Study Design**

- Repeat baseline scans only done in the first 15 patients enrolled in each arm

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