New Biochemical Markers for NET - Un Unmet Need

by

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Nashville Oct 2011
Cancer Biomarkers: Can we turn recent failures into success? (Diamandis, JNCI Aug 2010)

- NIH definition of a biomarker: “A characteristic that is objectivity measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention”

- No new major cancer biomarker has been approved for clinical use for at least 25 years!

- A handful cancer biomarkers are intended mainly for monitoring response to treatment of patients with advanced disease.

- Most biomarkers in clinical use are not suitable for population screening or for early diagnosis
Phases of Biomarker Development

1. Preclinical exploratory phase
2. Clinical assay and validation phase
3. Retrospective longitudinal clinical repository study
4. Prospective screening studies
5. Randomized controlled trials
Biomarkers in NETs

- Histopathology, tumor biology
- Circulating markers
- Response evaluation
- Circulating tumor cells

Molecular imaging
# Immunohistochemically Detected Neuroendocrine Markers

<table>
<thead>
<tr>
<th>Type of Marker</th>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytosolic</td>
<td>NSE, PGP 9.5</td>
</tr>
<tr>
<td>Related to secretory granules</td>
<td>Chromogranins</td>
</tr>
<tr>
<td>Related to synaptic vesicles</td>
<td>Synaptophysin, VMAT</td>
</tr>
<tr>
<td>Intermediate filaments</td>
<td>NF, CK HMW</td>
</tr>
<tr>
<td>Adhesion molecules</td>
<td>N-CAM</td>
</tr>
<tr>
<td>Proliferation</td>
<td>Ki67 (MIB1)</td>
</tr>
<tr>
<td>Grade</td>
<td>Ki67 Index (%)</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
</tr>
<tr>
<td>G1</td>
<td>&lt;2</td>
</tr>
<tr>
<td>G2</td>
<td>3–20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

Ki67 index (% of positive cells per 2000 counted cells)

Mitotic count (10 HPF)
### Neuroendocrine Neoplasms: NENs of the Gastroenteropancreatic (GEP) System

<table>
<thead>
<tr>
<th>WHO 1980</th>
<th>WHO 2000</th>
<th>WHO 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Carcinoid</strong></td>
<td>1. Well-differentiated endocrine tumor (WDET)*</td>
<td>1. NET G1 (carcinoid)</td>
</tr>
<tr>
<td></td>
<td>2. Well-differentiated endocrine carcinoma (WDEC)*</td>
<td>2. NET G2*</td>
</tr>
<tr>
<td></td>
<td>3. Poorly differentiated endocrine carcinoma/small-cell carcinoma (PDEC)</td>
<td>3. NEC G3 large-cell or small-cell type</td>
</tr>
<tr>
<td><strong>III. Mixed forms carcinoid-adenocarcinoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IV. Pseudotumor lesions</strong></td>
<td>5. Tumor-like lesions (TLL)</td>
<td>5. Hyperplastic and preneoplastic lesions</td>
</tr>
</tbody>
</table>

NET, neuroendocrine tumor—well differentiated; NEC, neuroendocrine carcinoma—poorly differentiated; G, Grade

*Some numerals are purple. Are they to show which are as described in bullet point below?*

- If the Ki67 index exceeds 20%, this NET may be labeled G3.
Correlation of WHO Classification (2004) and Ki67 With Survival

Receptors (targets for diagnosis and therapy)

- Somatostatin receptors
- Dopamine receptors
- Interferon receptors
- Growth factor receptors
Somatostatin Receptor Subtypes

Case 1

CgA

sst_1

sst_2

sst_3

sst_4

sst_5

Case 2

CgA

sst_1

sst_2

sst_3

sst_4

sst_5
Somatostatin receptor subtype and dopamine D\textsubscript{2} receptor mRNA levels in GEP NETs

\[ n = 35 \text{ GEP NETs (19 pancreatic and 16 intestinal) RT-PCR} \]
## Growth factors in neuroendocrine tumors

<table>
<thead>
<tr>
<th></th>
<th>Carcinoids tumors stroma</th>
<th>Carcinoids tumors tumor</th>
<th>Endocrine pancreatic tumors stroma</th>
<th>Endocrine pancreatic tumors tumor</th>
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</thead>
<tbody>
<tr>
<td>PDGF</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>PDGF-βR</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>PDGF-αR</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>TGF-β₁</td>
<td>(+)</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>TGF-β₂</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>TGF-β₃</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LTBP</td>
<td>+++</td>
<td>(+)</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>TGF-βRII</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>b-FGF</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>b-FGF R</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>TGF-α</td>
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<tr>
<td>EGF-R</td>
<td>+</td>
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<tr>
<td>IGF-1</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>VEGF</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>FLt-1</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>
Biomarkers in NET

- CgA is the best available biomarker for diagnosis of NET
  - Elevated CgA may correlate with tumor progression
  - CgA is elevated 80%–100% of the time in NET

- NSE is also expressed in NET
  - Not used as commonly as CgA
  - Often elevated in poorly differentiated tumors

- Other biomarkers are available, but few have achieved widespread acceptance

- New biomarkers in NET are needed to provide better diagnostic and prognostic information


5-HIAA = 5-hydroxy-3-indoleacetic acid
5-HT = serotonin
GHRH = gonadotropin hormone release hormone
hCG α/β = human chorionic gonadotropin
ANP/BNP = atrial natriuretic peptide and brain/ventricular natriuretic peptide
NSE = neuron-specific enolase
PYY = peptide YY
The Chromogranin Family

- Chromogranin A (CgA)
- Chromogranin B (CgB)
- Secretogranin II (CgC)
- Secretogranin III (1B1075)
- Secretogranin IV (HISL-19)
- Secretogranin V (7B2)
- Secretogranin VI (NESP55)
Focus on Chromogranin A

Chromogranin A–Related Peptides

- Chromostatin
- WE14
- Catestatin
- GE25
- Parstatin
- Chromasins I
- Chromasins II
- Vasostatins
- Pancreastatins

Carcinoid
EPT
MEN1
PHEO
Normal

Chromogranin A and B Levels in NET Patients

p-CgA

p-CgB

Correlation of Baseline CgA Levels With Survival

N=39

P=0.02

Chromogranin A μg/L

- <100 μg/L, n = 6
- 100–1000 μg/L, n = 16
- >1000 μg/L, n = 16
Tumor Genetics and biology
DNA Microarray Analysis:

GI Carcinoids and PNETs Cluster independently

Duerr et al. Endocr Rel Cancer. 2008
Micro arrays of normal EC-cells and carcinoid tumors

Leja et al. 2008
Benign and malignant PNETs cluster independently

- 112 genes differentially expressed with P < 0.05

- “benign” cluster
  - 3/3 WDETs – benign
  - 8/9 WDETs – LGM
  - 1/7 WDEC

- “malignant” cluster
  - 6/7 WDECs
  - 1/9 WDETs - LGM

Specific markers for decisions on treatment
Role of MGMT in Modulating Temozolomide Sensitivity

- Absence of MGMT expression appears to be key to realizing benefit with Temozolomide
  - MGMT deficiency was observed in 19 of 37 (51%) pancreatic neuroendocrine tumors and 0 of 60 (0%) GI NETs
  - This correlates with treatment response

O\textsuperscript{6}-methylguanine DNA methyltransferase (MGMT\textsuperscript{*}) expression\textsuperscript{#} may predict response to temozolomide in GEP NETs

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Response (RECIST)</th>
<th>Response (CgA)</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMT positive</td>
<td>16</td>
<td>0/16</td>
<td>0/10</td>
<td>9.25</td>
<td>14</td>
</tr>
<tr>
<td>MGMT Negative</td>
<td>5</td>
<td>4/5**</td>
<td>4/5</td>
<td>19</td>
<td>NR</td>
</tr>
</tbody>
</table>

** p<0.05
# MGMT expression studied by IHC
NR = not reached
* MGMT is a DNA repair enzyme believed to induce cancer cell resistance to O\textsuperscript{6}-alkylating agents like temozolomide

mTOR Signaling Pathways

Receptor Tyrosine Kinase

Nutrients & Metabolites

IRS-1 P
PI3K
Grb
SOS
RAS

AKT

TSC1/2

Rheb

mTORC1

Protein Synthesis

p70S6K P

HIF-1α

Glut 1

VEGF, PDGF-β

Everolimus

4EBP1 P
eIF4E

Cyclin D, p27

Growth & Proliferation

Metabolism

Angiogenesis
Tuberous sclerosis 2 (TSC2) protein expression and its correlation with survival in pancreatic endocrine tumors (PETs)

Missiaglia E et al. JCO 2010;28:245-255

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Phosphatase and tensin homolog (PTEN) protein expression and its correlation with survival in pancreatic endocrine tumors (PETs)

Missiaglia E et al. JCO 2010;28:245-255
PTEN Expression Based on WHO Classification (p=8.667)
PTEN Expression Based on TNM Classification Respectively Stage Disease (p=0.1452)
New Biochemical Markers
## Tumor marker genes in classical midgut carcinoids

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GR1A2</td>
<td>Glutamate receptor, ionotropic AMPA2</td>
</tr>
<tr>
<td>GPR112</td>
<td>G-protein compled receptor 112</td>
</tr>
<tr>
<td>PNMA2</td>
<td>Paraneoplastic antigen MA2</td>
</tr>
<tr>
<td>SPOCK1</td>
<td>Sparc, osteonectin (proteoglycan)</td>
</tr>
<tr>
<td>SERPINA10</td>
<td>Alpha -1 antiproteinase, antitrypsin</td>
</tr>
<tr>
<td>OR51E1</td>
<td>Olfactory receptor, family 51 subfamily E, member 1</td>
</tr>
</tbody>
</table>

*Leja et al. 2008*
PNMA-2
PNMA-2

A

B

Proportion PFS

Proportion Recurrence Free Survival

< cut off

> cut off

p-value = 0.006

p-value = 0.006

Months

Months
Olfactory receptor, family 51, subfamily E, member 1 (OR51E1)

OR51E1 encodes a G protein-coupled receptor, which belongs to the olfactory receptor family. The discovery of a family of odorant/olfactory receptors in the olfactory epithelium by Buck and Axel was the main event for understanding olfactory function (Buck & Axel, Cell, 1991).

Then olfactory genes have been characterized in a number of non olfactory tissues. Richard Axel & Linda B. Buck got the Nobel prize in physiology or medicine in 2004.

We identified restricted OR51E1 expression in normal EC cells and SI-NET cells by EST database analysis (Vasmatzis et al, Bioinformatics 2007, 23 1348-1355). The analysis confirmed restricted expression in normal prostate, prostate cancer, lung cancer and colon cancer cells.

The restricted expression in normal tissues made OR51E1 a novel cancer biomarker for SI-NET.

However, we did not detect protein expression neither in normal SI tissue or SI-NET tissue and we blamed law quality of the available antibodies.
Olfactory receptors: G protein-couple receptors and beyond

**OR51E1 Chain 1-327 Potential domains**

Topological domain 1-27 ExtraCell 27nt
1 Transmembrane 28-48 Helical 21nt
Topological domain 49-56 Cytoplasmic 8nt
2 Transmembrane 56-77 Helical 21nt
Topological domain 78-101 ExtraCell 24nt
3 Transmembrane 102-122 Helical 21nt
Topological domain 123-141 Cytoplasmic 19nt
4 Transmembrane 142-162 Helical 21nt
Topological domain 163-198 ExtraCell 36nt
5 Transmembrane 199-219 Helical 21nt
Topological domain 220-238 Cytoplasmic 19nt
6 Transmembrane 239-259 Helical 21nt
Topological domain 260-274 ExtraCell 15nt
7 Transmembrane 275-295 Helical 21nt
Topological domain 296-317 Cytoplasmic 19nt

**Amino acid modifications**
Glycosilation 7 N-linked (GlcNAc...) 1
Glycosylation 90 N-linked (GlcNAc...) 1
Disulfide bond 99<191> By similarity
**OR51E1 QRT-PCR Analysis**

- **BON**, pancreatic carcinoid
- **QGP1**, pancreatic carcinoma
- **KRJ1**, midgut carcinoid
- **CNDT2.5**, midgut carcinoid
- **NCI-H720**, lung carcinoid
- **NCI-H727**, lung carcinoid
- **A549**, lung adenocarcinoma
- **SH-SY5Y**, neuroblastoma
- **SKNSH**, neuroblastoma
- **mel526**, melanoma
- **NCI-H727**, lung carcinoid
- **LNCaP**, prostate carcinoma
- **HT29**, colon adenocarcinoma
- **Daudi**, Burkitt's lymphoma
- **1064SK**, skin fibroblasts
OR51E1 IHC on PE tumor slides

Normal Ileum (-)
43 Primary SI-NETs (+)
5 Lymph Node Metastases (3+ & 2-)
23 Mesentery Metastases (+)
17 Liver Metastases (12+ & 5-)
MicroRNAs (miRs) are post-transcriptional regulators, controlling cell proliferation, apoptosis and differentiation in a variety of cells.

miRs are expressed by non-coding genes as pri-mRNA.

Drosha cleaves both strands of pri-miR to release a stem loop circa 70 bp.

The pre-miR is exported from the nucleus to the cytoplasm by Exportin-5.

Dicer cleaves the pre-miR in the cytoplasm, to release about 22 bp RNA and then the short sequence will be incorporated into miRISC.

MiRISC guides miR to the target mRNA, controlling either mRNA degradation or translational inhibition.

From, Bioinformation, 2010; 5(6): 271-276
SI-NETs MiR expression

Little evidence of miRNA expression/deregulation in SI-NET has been reported to date and we decided to perform the first genome wide Affymetrix miR array analysis.

We clearly detected 33 differentially expressed miRs in mesentery and liver metastases compared to primary tumors.

The upregulated miRs are indicated in yellow and the downregulated miRs are indicated in blue.

We then selected 9 miRs for further analysis and they are marked by a red asterisk.
SI-NETs QRT-PCR Analysis

Downregulated miR expression in mesentery and liver metastases compared to primary tumors

We used normal laser-microdissected EC cells as references (Prof. Ricardo V. Lloyd)

EC = enterochromaffin cells
P = primary tumors
M = mesentery metastases
L = liver metastases

*P < 0.05
Northern blot analysis on SI-NETs

Total RNA hybridized with $^{32}$P radiolabeled RNA probes to detected miRs

MiR-182 and -183 upregulated in metastatic stage compared to primary tumors

MiR-31 and -133a downregulated in metastatic stage compared to primary tumors
Conclusions

The expression of 4 miRs (miR-96, -182, -183 and -196a) is significantly upregulated in metastatic diseases compared to primary tumors, while the expression of 3 miRs (miR-31, -133a and -215) is significantly downregulated.

Ongoing

We are verifying miR targets of tumor miRs, selected by bioinformatics algorithms and published microarray analysis (Leja et al, Modern pathology 2009).

One of the main goals is to screen neuroendocrine cell lines (CNDT2.5, KRJ-1, QGP-1, NCI-H720 and NCI-H727), which have been microRNA profiled as well, to discriminate miR targets effects on cell biology, i.e. miRNA and target protein levels alteration.

Future

The final goal at the moment is to develop the selected microRNAs as novel serum/plasma markers creating less invasive tests for the patients to monitor cancer.
## Potential target genes of the selected miRs

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Gene Symbol</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-96</td>
<td>BAI3</td>
<td>G-protein coupled receptor protein signaling pathway</td>
</tr>
<tr>
<td></td>
<td>EFNA5</td>
<td>cell-cell signaling, cell differentiation</td>
</tr>
<tr>
<td></td>
<td>RAPGEF4</td>
<td>G-protein coupled receptor protein signaling pathway</td>
</tr>
<tr>
<td>miR-182</td>
<td>FZD5</td>
<td>apoptosis, negative regulation of cell proliferation</td>
</tr>
<tr>
<td></td>
<td>MAPRE2</td>
<td>signal transduction, cell proliferation</td>
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<tr>
<td></td>
<td>SCN2A</td>
<td>apoptosis, transmembrane transport</td>
</tr>
<tr>
<td>miR-183</td>
<td>CELSR3</td>
<td>G-protein coupled receptor protein signaling pathway</td>
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<tr>
<td></td>
<td>MAPK8IP1</td>
<td>signal transduction, anti-apoptosis, signal transduction</td>
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<tr>
<td></td>
<td>PDE4D</td>
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<tr>
<td>miR-196a</td>
<td>EPHA7</td>
<td>protein phosphorylation, positive regulation of apoptosis</td>
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<td></td>
<td>HOXB7</td>
<td>regulation of transcription, DNA-dependent</td>
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<td></td>
<td>PEG10</td>
<td>apoptosis, cell differentiation</td>
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<tr>
<td>miR-200a</td>
<td>EPHA7</td>
<td>transmembrane receptor protein tyrosine kinase signaling pathway</td>
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<td></td>
<td>KHDRBS2</td>
<td>regulation of transcription, DNA-dependent</td>
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<tr>
<td></td>
<td>NEK6</td>
<td>apoptosis, signal transduction</td>
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</tbody>
</table>
### Potential target genes of the selected miRs

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Gene Symbol</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-31</td>
<td>CTNND2</td>
<td>signal transduction, regulation of transcription</td>
</tr>
<tr>
<td></td>
<td>NR5A2</td>
<td>regulation of transcription, regulation of cell proliferation</td>
</tr>
<tr>
<td></td>
<td>RGS4</td>
<td>regulation of G-protein coupled receptor protein signaling pathway</td>
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<tr>
<td>miR-129-5p</td>
<td>DCX</td>
<td>intracellular signal transduction</td>
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<td></td>
<td>RUNX1T1</td>
<td>regulation of transcription, DNA-dependent</td>
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<td>ZNF618</td>
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<td>miR-133a</td>
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<td>ENPEP</td>
<td>cell proliferation</td>
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<td>transmembrane receptor protein tyrosine kinase signaling pathway</td>
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<tr>
<td>miR-245</td>
<td>PTPRT</td>
<td>protein dephosphorylation</td>
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<tr>
<td></td>
<td>RUNX1T1</td>
<td>regulation of transcription, DNA-dependent</td>
</tr>
</tbody>
</table>
Proximity ligation assay (PLA)

PLA is an immunoassay where pairs of oligonucleotide-labeled antibodies are employed to detect an antigen of interest to identify novel biomarkers.

Microparticle based PLA method

Samples are incubated with antibodies preimmobilized on microparticles. B, next, microparticles are washed and incubated with pairs of PLA probes. C, finally, oligonucleotides on PLA probes are ligated upon proximal binding of a common antigen and addition of a connector oligonucleotide. This is followed by amplification and detection of the ligated products by quantitative real time PCR, the primers of which are indicated by arrows.

Darmanis S et al. Mol Cell Proteomics 2010;9:327-335
We analyzed the first PLA experiment, using 36 analytes at the beginning. Results were plotted using Random Forests, which is a kind of supervised multivariate analysis.

Random Forests (or Random forest) is an ensemble classifier consisting of many decision trees and outputs the class that is the mode of the class's output by individual trees. Leo Breiman and Adele Cutler developed the algorithm for inducing a random forest and today "Random Forests" is their trademark.

First we separated the data into treated and non-treated patients. We compared all the 5 groups to each other (G1 vs G2 vs G3 vs HC vs IBD), 3 groups (all patients"G" vs HC vs IBD) and finally each of the three patient groups to each other (G1 vs G2 vs G3)

G1 = Midgut primary tumors, G2= Limph node metastasis, G3= Liver Metastases IBD = Inflammatory Bowel Diseases and HC= Healthy Controls
Non treated samples

All groups

G vs HC vs IBD

G1 vs G2 vs G3
Non Treated Samples & Treated Samples
Preliminary Results from the Pilot Experiment

Our bioinformatician has only looked at the samples before treatment and considered different mergers of the five different sample types G1, G2, G3, IBD and HC. He has studied estimates of the false alarm rate, the false negative rate and the total error rate (different columns). More work needs to be done to confirm and hopefully improve the performances and the proteins identified as most outstanding.

* The average discrimination error rate estimates for the different subtasks studied range between 15% and 32% but for some case the probability of missing a tumois around 50% while the probability of a false alarm is much lower.

* The three easiest subtasks found so far seem to be discrimination between IBD and tumors (error rate estimate 15%) and discrimination between G2 (lymph) and IBD (17%) and discrimination between G3 (liver) and HC (19%).

* For discrimination between IBD and tumor (G1+G2+G3)r, interesting proteins are Cystatin B and Cathepsin.

* For discrimination between G2 (lymph) and IBD, interesting proteins are Cystatin B, Cathepsin S and E-selectin.

* For discrimination between G3 (liver) and HC, interesting proteins are GDF15, Kallikrein 6 and EGF.

* Discrimination between tumors and HC+IBD (merged together as controls) suggests that Cystatin B, Kakekrein and HCC-4 are important (I do not think that is a good screening, VG).

* One of the most difficult subtasks so far is discrimination between G2 (lymph) and HC: Here EGF seems to be the major player for the discrimination but the estimate for the probability of miss is 48%.

* Another difficult subtasks is discrimination between the non-tumors (HC+IBD) and G1 (primary) and G2 (lymph) studied separately. In both case, the probability of missing the tumor is around 50% with the current settings.
Specific Isotopes for NETs

- $^{11}$C-5HTP (hydroxytryptophan)
- $^{11}$C-Dopamine
- $^{18}$F-Dopamine
- $^{68}$Ga-DOTA-octreotide
- $^{99}$Tc EDDA-HYNIC-octreotide
- [Lys40(Ahx-DTPA-$^{111}$In)NH2]-Exendin-4 (GLP-1)
$^{68}$Ga-DOTATOC

- $^{68}$Ga positron emitter
- Half-life 68 min
- Generator production
- Better spatial resolution with PET than SPECT
- Examination 1 h after injection—logistical benefits
NET—Small Intestine
Fig 3. (A) Computed tomography (CT) scan, (B) somatostatin receptor scintigraphy (SRS), (C) 18F-dihydroxy-phenyl-alanine (18F-DOPA) positron emission tomography (PET), and (D) 11C-5-hydroxy-tryptophan (11C-5-HTP) PET of a 54-year-old male patient with metastatic islet cell tumor.

PET/CT With $^{11}$C-5-HTP
New markers for molecular imaging
Conclusions

• Neuroendocrine tumors offer unique possibilities for development of new biomarkers.
• There is an unmet need for development of new sensitive markers for early diagnosis and recurrence after surgery.
• There is an urgent need for biomarkers of treatment response evaluation (expensive therapies – side effects)
• The ultimate goal will be genome wide screening of each tumor to define targets for therapy aiming at personalized medicine (next generation sequencing.)
Thank you!

Centre of Excellence Endocrine Tumors, Uppsala University
http://www.endocrinetumors.org/