New Research Horizons: Challenges and Opportunities

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What is “hot” in medicine (oncology)?

NCI Provocative Questions

- How do cancer-specific subcellular pathognomonic structures develop, what is their function, and can they be a source of novel therapeutic targets?
- What are the predictive biomarkers for the onset of immune-related adverse events associated with check-point inhibition, and are they related to markers for efficacy?
- Can we develop bifunctional small molecules that will couple oncoproteins or other cancer causing molecules of interest to inactivating processes such as degradation and achieve tissue-specific loss of function?
- How do microbiota affect response to cancer therapies?
- Through what mechanisms do diet and nutritional interventions affect the response to cancer treatment?
- What are the molecular and/or cellular mechanisms that underlie the development of cancer therapy-induced severe adverse sequelae?
NCI Provocative Questions

- What molecular mechanism influence disease penetrance in individuals who inherit a cancer susceptibility gene?
- How do variations in immune function caused by comorbidities or observed among different populations affect response to cancer therapy?
- Do genetic interactions between germline variations and somatic mutations contribute to differences in tumor evolution or response to therapy?
- Can we develop tools to directly change the expression or function of multiple chosen genes simultaneously and use these tools to study range of changes important for human cancer?
- How can mitochondrial heterogeneity influence tumorigenesis or progression?
- How do circadian processes affect tumor development, progression, and response to therapy?

Where is medical physics?

What could we do in advanced disease?

Quantitative Total Bone Imaging (QTBI)
We can develop novel technologies!

Repeatability of NaF PET/CT

- Multicenter trial of metastatic castrate-resistant prostate cancer patients received pre-treatment test-retest ¹⁸F-NaF PET/CT scans

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients</th>
<th>Bone lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Wisconsin Carbone Cancer Center</td>
<td>18</td>
<td>265</td>
</tr>
<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>11</td>
<td>78</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>6</td>
<td>68</td>
</tr>
<tr>
<td>All</td>
<td>35</td>
<td>411</td>
</tr>
</tbody>
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Test/retest scans (3-5 days apart)

Standardized Uptake Value (SUV) metrics extracted from an ROI

- \( \text{SUV}_{\text{max}} \) – maximum uptake
- \( \text{SUV}_{\text{mean}} \) – average uptake
- \( \text{SUV}_{\text{total}} \) – total uptake

What is our quantitative accuracy?
What is our quantitative accuracy?

Limits of agreement define response

Local disease heterogeneity
40/43 patients exhibit response heterogeneity regardless of burden.

We can see things that no-one has seen before!

Non-favorable response dominates progression events!

We can provide unique insight into disease!

From a single scan – LOTS of data!
Data is the future...

We are getting to know how to deal with big data!

Lots of data – we’ve seen it before...

But how do PHYSICISTS deal with such big data?

Physicists want to understand!
What about medical physicists?

Adhikari and Jeraj 2012, Phys Med Biol 57: 6103

Oh no, now we have to deal with BIOLOGY...

But that is much harder...

Biology enters the stage...

Biological complexity by far exceeds physical complexity!

“Bottom-Up” vs “Top-down” approach

How and what can we approximate?

We are not biologists...

(how much of the biological language do we speak)?

It requires rethinking what medical physics is...

Should we expand beyond physics? How?

Should we partner? How?

PQ for Med Phys (in Oncology)

- Science Council/WG FUTURE initiative
- Goal: to define highest-level problems in oncology that medical physics should attack
- Two-day meeting on Oct 31/Nov 1 2016 in Boston
- Modelled after NCI's Provocative Questions
- Very diverse panel
- Additional input from AAPM membership at large
Provocative Questions for Medical Physics Symposium
Monday, 4:30-6pm

1. How do we develop physical models of “tissue homeostasis” – maintenance of stable tissue properties despite inputs (e.g., structure, spatial relationships, ECM, hormones, cytokines, etc.)? How do we quantitatively analyze between different inputs?

2. How do we measure treatment effects (e.g., reduced vascularity in anti-angiogenic treatments), which are necessary, but not sufficient for successful treatment? How do we treat “tumor homeostasis” to the tissue (tumor and host) – meeting the non-tumor phenotypic state? What is the role of information dynamics in cancer treatment (e.g., cancer attractor approach)?

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