Innovating with Existing Drugs and Nutraceuticals

Opening Remarks

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Problem and the Opportunity

- **Problem**: There remain large unmet needs in medicine, since many therapies are expensive, quite toxic, or only modestly effective.

- **Opportunity**: There exist scientifically promising ideas for new treatments which are not being developed largely because they lack sufficient financial incentive (financial orphans).
Typical new drug development path

- Pre-Clinical

PROMISING IDEAS

- ROI?
  - Yes
  - No

PROMISING IDEAS

- Pharma
  - Clinical Trials

ROI?

- Patent
- Market size
- Chances of successful development
- Reimbursement
Existing drugs

- Pre-Clinical
- Epidemiology
- Case Reports

PROMISING IDEAS

ROI?

Yes  No

- Patent
- Market size
- Chances of successful development
- Reimbursement

Pharma

Clinical Trials
Financial Orphan Categories

- Approved drugs that could be repurposed
- Nutraceuticals
- Lifestyle interventions
Recognition of Problem

• Non-profits
  • GlobalCures
  • Anticancer Fund (ReDO project)
  • Cures within Reach

• Government
  • NCATS/NIH/FDA/CMS

• Academia
Clinical Development of Financial orphans

Advantages
- Affordability
- Toxicity (typically well-known)
- Wide availability

Rapid, worldwide impact

Challenges
- Interventions and prioritization
- Recruiting MD investigators for studies
- Funding
## Interventions and prioritization

<table>
<thead>
<tr>
<th></th>
<th>Non-cancer drugs</th>
<th>Cancer drugs</th>
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<tbody>
<tr>
<td></td>
<td>Common drugs</td>
<td>Uncommon drugs</td>
</tr>
<tr>
<td>Epidemiology studies</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pre-clinical research: in silico/wet lab</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Case reports/ limited clinical trials</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
Uncommon drugs

- Fenbendazole
- Melatonin
- Chloroquine
- Mifepristone
- Disulfiram
- Itraconazole
- IL-6 antagonists
- Fenbendazole
Cancer drugs

- HDACi
- Cytoxan
- Retinoids
- IL-2
- Capecitabine
Too many options and no consensus on treatment strategy!
Scientific framework for prioritizing ideas (for cancer)
Mutations give tumor cells a growth advantage over non-tumor cells.

Adaptation response leads to treatment resistance and cell survival.

Injury response leads to growth enhancing microenvironment and can awaken dormant mets.

Tumor cells are fertilized by the injury response and replenish injured tissue and provide a microenvironment conducive to tumor proliferation and spread.
Scientific Framework

- Uncontrolled Growth
- Cellular Stress
- Adaptation Response
  - Cell death
  - Injury Response
- Cell survival
- Growth Factors
  - Immune Suppression
  - Fibrosis
- Tumor Growth and Metastasis

Cancer Treatments

- Mutations give tumor cells a growth advantage over non-tumor cells
- Adaptation response can lead to treatment resistance and cell survival
- Injury response leads to growth enhancing microenvironment and can awaken dormant mets
- Tumor cells are fertilized by the injury response that feeds injured tissue (tumor and non-tumor) and provides a microenvironment conducive to tumor proliferation and spread
Injury Response

Hemostasis

Infection?

Yes

Immune Activation and Sterilization

No

Immune Suppression

Tissue regeneration and remodeling

Tumor Growth and Metastasis

Platelet degranulation
Mast cells (histamine)
Neurons (catecholamines)

Neutrophils
NK Cells
Macrophages
Dendritic Cells
T Cells

MDSCs
Tregs
M2 macrophages

Diminish injury response

- Reduce chemokines, growth factors
- Mitigate immune suppression
- Stop epithelial to mesenchymal transition
- Reduce stem cell population
### Blocking the Injury Response

<table>
<thead>
<tr>
<th>Cellular Component</th>
<th>Mediator</th>
<th>Drug</th>
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</thead>
<tbody>
<tr>
<td>Dead Tumor Cells</td>
<td>Adenosine</td>
<td>Pentoxifylline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caffeine</td>
</tr>
<tr>
<td>Platelets</td>
<td>PGE2</td>
<td>NSAIDs (aspirin, ketorolac)</td>
</tr>
<tr>
<td></td>
<td>PDGF, VEGF, HGF, FGF, TGF-β</td>
<td>Clopidogrel, EPA/DHA</td>
</tr>
<tr>
<td></td>
<td>Lysophosphatidic Acid (LPA)</td>
<td></td>
</tr>
<tr>
<td>Mast Cells</td>
<td>Histamine; renin</td>
<td>Cimetidine; ARBs</td>
</tr>
<tr>
<td>Neurons</td>
<td>Catecholamines</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Immune Cells</td>
<td>IL-6, TGF-β, IL-10, VEGF</td>
<td>AHCC, PSK, Maitake D extract, flu vaccine, arginine + omega 3; IL-6 antagonists, NSAIDs, beta blocker, sildenafil, low dose cyclophosphamide, mifepristone</td>
</tr>
</tbody>
</table>
Key immunotherapy steps

- Initiate immune response to tumor
- Localize effector response to tumor
- Maintain effector response
- Create memory
- Reverse tumor induced immunosuppression
Reverse tumor induced immunosuppression

Key immunotherapy steps

- Reduce tumor burden: kill tumor cells or surgically remove them
- Reduce production of or release of cytokines from tumor cell or other cells in injury response
- Neutralize action of soluble factors/cytokines (sMICA/B, TGF-β, IL-6) and metabolites (adenosine, PGE2, catecholamines, histamine)
- Impact suppressor cell populations (Tregs, MDSCs, M2 macrophages): reduce number, antagonize function, cause differentiation or prevent tumor localization
- Present danger signals in tumor vicinity
Reverse tumor induced immunosuppression

Impact suppressor cell populations (Tregs, MDSCs, M2 macrophages):
- Reduce number, antagonize function,
- Cause differentiation or prevent tumor localization
- Neutralize action of soluble factors/cytokines (sMICA/B, TGF-β, IL-6) and metabolites (adenosine, PGE2, catecholamines, histamine)
- Reduce production or release of cytokines from tumor cell or other cells in injury response

Present danger signals in tumor vicinity

Reduce tumor burden: kill tumor cells or surgically remove them

NSAIDs, vitamin D, ATRA, PDE5 inhibitors, capecitabine

Caffeine, A2AR antagonists

Beta blockers

Cimetidine

Tocilizumab, siltuximab

Cyclophosphamide, temozolomide

PSK

Key immunotherapy steps
Prioritizing Ideas

- Fit with a scientific framework/mechanistic underpinning
- Level of evidence of data with weighting as follows: human phase II > phase I > case series > animal data
- Expected magnitude of increase in efficacy outcomes or improvement in QOL
- Anticipated, manageable and non-overlapping toxicities
- Biomarker for patient subset likely to benefit or early biomarker of long-term outcomes
- Cost
Recruiting investigators for trials

- Competition with pharma sponsored studies
- General disbelief
- Lack of awareness
- Pre-clinical and limited clinical data not strong enough to warrant further study
- Mechanism for cancer action may be not optimized
Funding

• Govt/philanthropy/foundations
• For profit and not for profit opportunities
Why now?

• Omics revolutions
  • parts list, pathways, diagnostics

• Big data/EMR
  • candidates, novel study methods, combo queries

• Technologies
  • Screens of existing drugs, use of single cell technologies for mechanistic insights

• Social media
  • Patient reported outcomes

Repurposed drug papers in Pubmed

Annual papers
Meeting Agenda

November 14, 2019
• Registration and Breakfast – 8:30 am
• Welcoming Remarks – 9:00 am
• Session 1: Identifying Drug Repurposing Opportunities – 9:25 am
• Session 2: Drug Repurposing for Cancer – 11:10 am
• Cocktails and Dinner – 6:00 pm

November 15, 2019
• Breakfast – 8:30 am
• Session 3: Drug Repurposing for Neurologic/Psychiatric Disease – 9:00 am
• Session 4: Innovations in Clinical Trial Design and Funding for Financial Orphan Research and Development – 10:10 am
• Conclusion/Round-Up – 11:40 am
• Lunch and Networking – 12:10 pm
Thanks

- Conference Ideas
  - GlobalCures - Vidula Sukhatme and volunteers
  - Anticancer Fund - Gauthier Bouche, Lydie Meheus

- Conference Support
  - Morningside Center for Innovative and Affordable Innovation
    - Emory leadership: President Sterk, EVPHA Jon Lewin and Provost McBride
    - Woodruff Foundation support via the WHSC
    - The Morningside Foundation
  - Emory Conference Center Subvention Fund
  - Colleagues at the Morningside Center and Emory
    - Lisa Carlson, Krista Charen, Michael Lowe, Vidula Sukhatme, Farah Chapes, Rebekah Hills

- Speakers and participants!
Concluding remarks and general Q and A

Vikas P. Sukhatme MD ScD
Goal: new (and affordable) treatments for patients

Provide enough evidence to change practice guidelines and to obtain insurance coverage
Perfect opportunity: wide availability of interventions!
Variants: real world data studies, participatory studies, point-of-care studies

“Distributed studies” for financial orphans

- Prescription drug intervention
  - Physician participation as a formal trial with IRB approval at each site
  - Patient requests transfer of medical record to him/her who transfers to a central site or requests MD to transfer data to a central site; MD is prescribing drugs off-label with informed consent but without IRB approval

- Non-prescription interventions
  - Patient requests medical record and then transfers relevant information to central site or requests MD to transfer such data to central site

NOTE: In both cases, central site has IRB approval for study and may conduct safety and feasibility study prior to overseeing a distributed study in the community.

Advantages:
- Real world data
- Cost-effective
- High throughput

Challenges (perspective of patient, physician, institution):
- Medico-legal
- Ethical
- Business: who pays; incentivizing community MDs
It takes a village to provide hope: one patient at a time

Modified from Dec 5-6, 2019 NIH conference agenda on Repurposing Off-Patent Drugs
Government commits $1 billion annually for 10 years to clear backlog of financial orphan opportunities