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Prioritizing targeted cancer therapies with CDGnet

Panel - The National Cancer Institute's Informatics Technology for Cancer Research Program: Building a Community of Practice in Cancer Informatics

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#AMIA2019

Disclosure

I and my spouse/partner have no relevant relationships with commercial interests to disclose.

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Project goal

Build a tool – **CDGnet** (Cancer Drug Gene networks) – to help researchers and eventually clinicians expand the number of targeted therapies available for individuals with cancer who have specific mutations (DNA changes) or genes/proteins that are overexpressed.

Precision oncology framework

Precision oncology refers to tailoring interventions to patients in ways that go beyond traditional characteristics of age, sex, disease, symptoms etc by considering biomarkers.

Biomarkers may be:

- genetic characteristics: can be either *germline* (inherited, in normal tissue) or *somatic* (in cancer cells but not normal tissue)
- mRNA or protein expression values: refer to expression in tumors, either in comparison to other tumors or to adjacent normal tissues

Tumor molecular profiling and targeted therapies

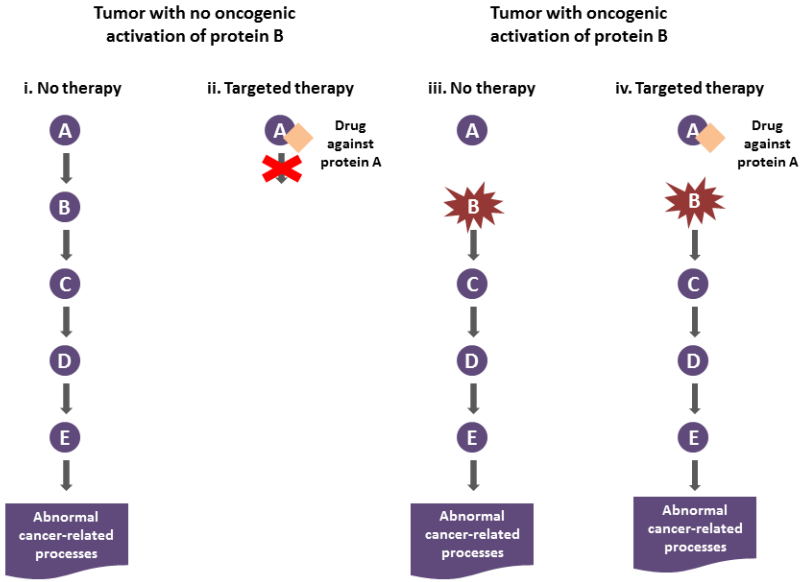
It is now routine to perform molecular profiling in certain tumor types to check for specific molecular features at diagnosis to decide on a targeted treatment plan (e.g. HER2+ breast cancer and trastuzumab)

In many cases tumor molecular profiling is used after a patient has progressed on multiple lines of therapy and/or has few/no therapy options left.

- Patient may then receive an off-label therapy that is prescribed for their alteration in another tumor type
- Our goal with CDGnet is to expand the number of possible targeted therapies and prioritize them using drug-gene network approaches by incorporating biological information

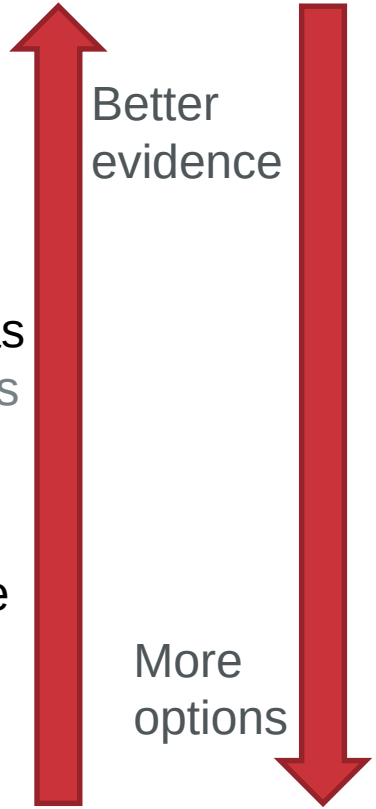
How do we include pathway information?

Look at downstream targets of oncogenes

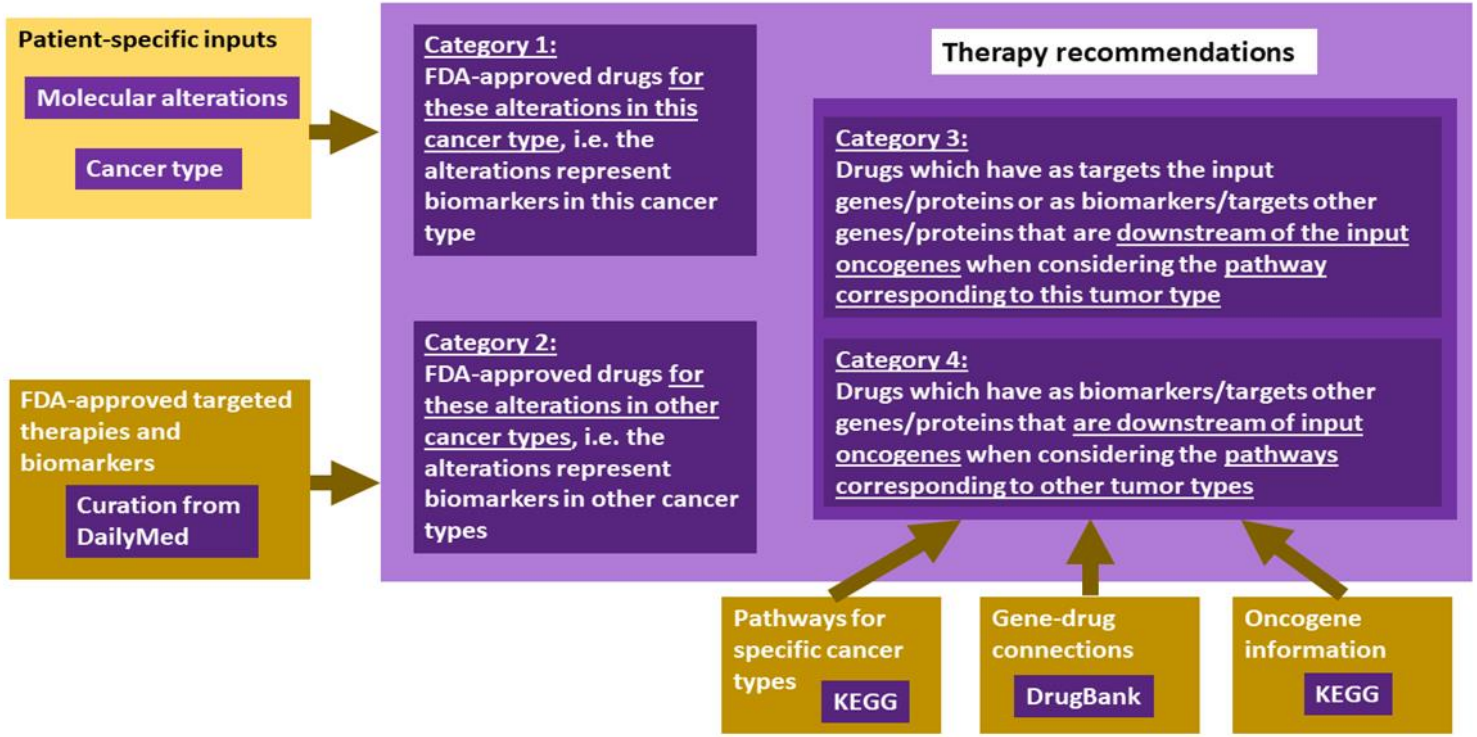


Therapy prioritization: 4 categories

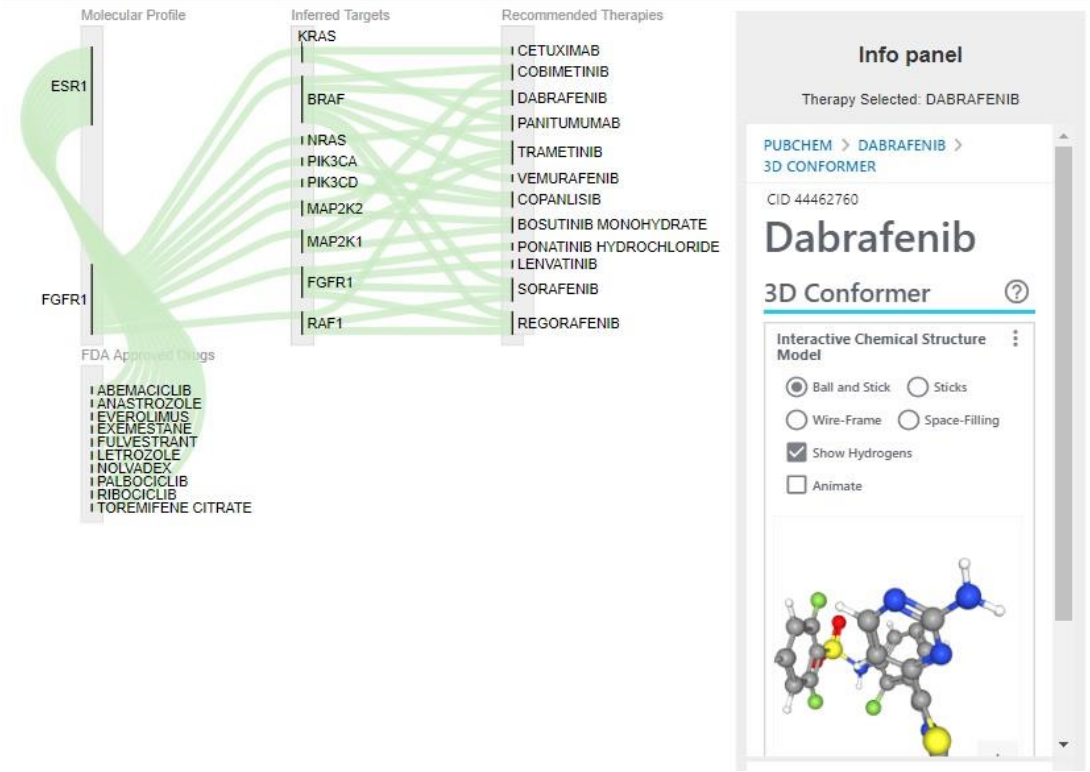
1. FDA-approved drugs for which the patient's alterations/genes/proteins are biomarkers in their tumor type
2. FDA-approved drugs for which the patient's alterations/genes/proteins are biomarkers in other tumor types
3. Drugs which have as targets these alterations/genes/proteins or as biomarkers/targets others that are downstream of input oncogenes when considering the pathway corresponding to this tumor type.
4. Drugs which have as targets/biomarkers either these alterations/genes/proteins or as biomarkers/targets others that are downstream of input oncogenes when considering the pathways corresponding to other tumor types.



General approach and data sources



CDGnet flow diagram example for category 3 recommendations



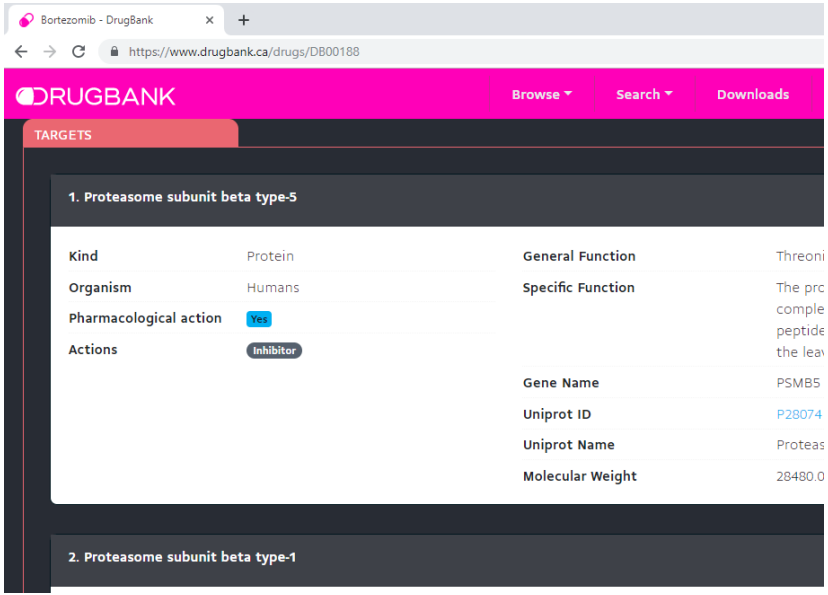
epiviz.cbcb.umd.edu/shiny/CDGnet/

How did we choose the pathways?

- We are currently using KEGG pathways but considering alternatives
- **Benefits:**
  - Well-known, include pathways for many individual cancers
  - Expert-curated pathways
- **Issues:**
  - May not always agree with papers chosen by curators
  - Not all cancer types included
  - Due to KEGG's policy on data use, cannot easily download their pathways and need a complicated approach to pulling in their data
    - This approach makes it difficult to perform updates and harder for others to reproduce our work

How did we choose the drug targets?

- We considered the DrugBank database, due to its comprehensiveness, expert-curation, and ease-of-use
- Note that DrugBank is not tissue-specific



How has being part of ITCR helped CDGnet development?

- Initial funding!
- Learning about other tools and collaborating with other investigators
  - Supplement to R21 to work with Tim Spicer and Louis Scampavia at Scripps – who was funded through the IMAT program – to integrate CDGnet into 3D spheroid/organoid high-throughput drug screening
  - Working with NDEx team to consider different pathways, share our pathways in NDEx, eventually integrate with Cytoscape
  - Exploring opportunities with CIViC and OncoMX
- Learning about best practices in reproducibility and training

Managing CDGnet as an open source software project

- Open-source projects are more than a code base!
- We have a code repository at https://github.com/SiminaB/CDGnet and a web application at http://epiviz.cbcb.umd.edu/shiny/CDGnet/
  - Currently do not have automatic updating
- Github repository includes README file, as well as:
  - Code of conduct – Many large projects and societies/scientific meetings now have this, to reduce possible harassment and bullying
  - Contribution guidelines and list of current contributors
  - Documentation that includes a step-by-step analysis for a patient use case scenario
  - R markdown notebook for a specific example
  - Example input files

Relevant links

- Shiny-based web application available at http://epiviz.cbcb.umd.edu/shiny/CDGnet/
- Code available at https://github.com/SiminaB/CDGnet and https://github.com/jkanche/nfpmShinyComponent (package for interactive visualization)
- Preprint available at https://www.biorxiv.org/content/10.1101/605261v1 (Kancherla, Rao et al)

Thank you!

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