Cancer treatment as a social phenomenon:

A network-based review of NCCN treatment guidelines

or:

[network ontology + oncology = network *onctology*]

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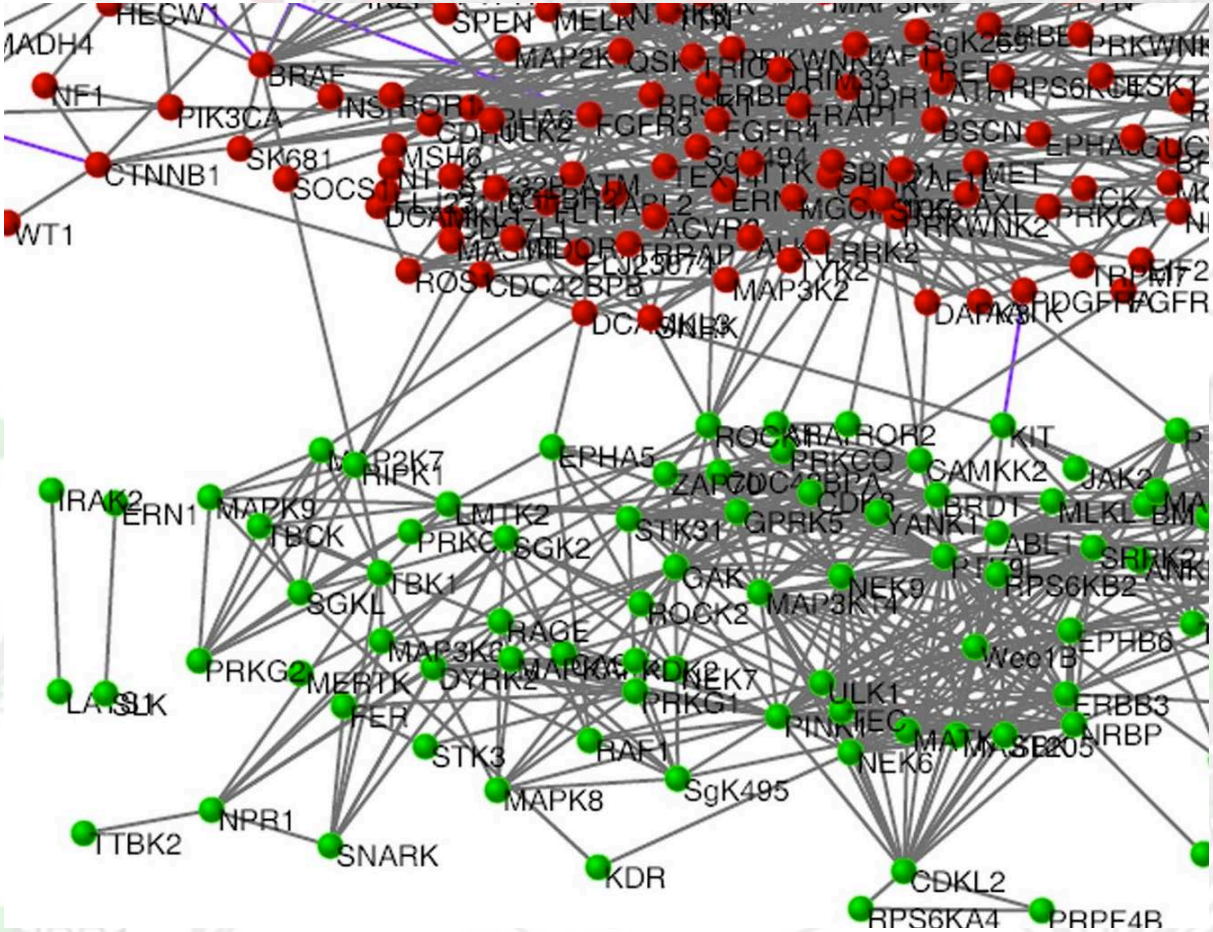
Networks & Cancer: Currently

- Networks no stranger to cancer
- Current networks are biological
- Relationships between different molecules *in human body*
- Nothing about business or social phenomena
  - Yet.

Networks & Cancer: Currently



Cui Q (2010) A Network of Cancer Genes with Co-Occurring and Anti-Co-Occurring Mutations. PLoS ONE 5(10): e13180. doi:10.1371/journal.pone.0013180

This study: Purpose

- Discover clinician biases
  - Studying clinician-chosen treatments, not necessarily biological responses
- Determine important drugs in supply chains
- Bibliographic correlations
- Determine cancers receiving more “attention” socially
- Framework for cancer treatment paradigms/future treatments

This study: Dataset

- Guidelines from National Comprehensive Cancer Network (NCCN) Template Series*
- All treatments for six disseminated cancers included
- 40 drugs total were involved
- Limited to freely available data

* “NCCN Templates”. National Comprehensive Cancer Network. http://www.nccn.org/ordertemplates/default.asp

Typical cancers

- Caused by plethora of genetic mutations
  - Most current cancer network research involves this ontology
- Non-mutated cells know when to die (apoptosis)
- Cancer cells don’t.
  - Not good.

Disseminated cancers

- Involve cells found throughout the body
  - I.e., leukemias and lymphomas
- Any out of control mutated cell line is therefore metastatic by nature
- Many, many kinds exist

Disseminated cancers

Examples for this study:

- AML = Acute Myelogenous Leuk.
- APL = Acute Promyelocytic Leuk.
- CLL = Chronic Lymphocytic Leuk./Lymph.
- CML = Chronic Myelogenous Leuk.
- MM = Multiple Myeloma (Lymph.)
- DBL = Diffuse B-Cell Lymph.
- ALL = Acute Lymphoblastic Leuk.

Typical cancer therapy (leukemias/lymphomas)

- Chemotherapy regimens, aka “chemo”
  - Combinations of drugs; monotherapy rare
- Many drugs used are as toxic to patient as they are the cancer (cytotoxic drugs)
  - Is the treatment worse than the disease?

Do you risk your life with conventional chemotherapy?

- **(Image: From a park in Belgrade, Serbia.)***
- **Death due to chemotherapy complications is coded in the ICD-10 as if it were death due to the cancer itself!****
- **Does typical chemotherapy risk lives?**

- Image credit: "Walking in this area, you risk your life". *Jordy's Big Adventure.* http://jordysbigadventure.files.wordpress.com/2010/06/belgrade-006small.jpg
- World Health Organization. Code no. Y43.9, "2012 causes of death casefinding list: Cancers". *International Classification of Disorders, 10th Ed.* Retrieved from SEER@Cancer.gov: http://seer.cancer.gov/tools/casefinding/codcase2012long.html

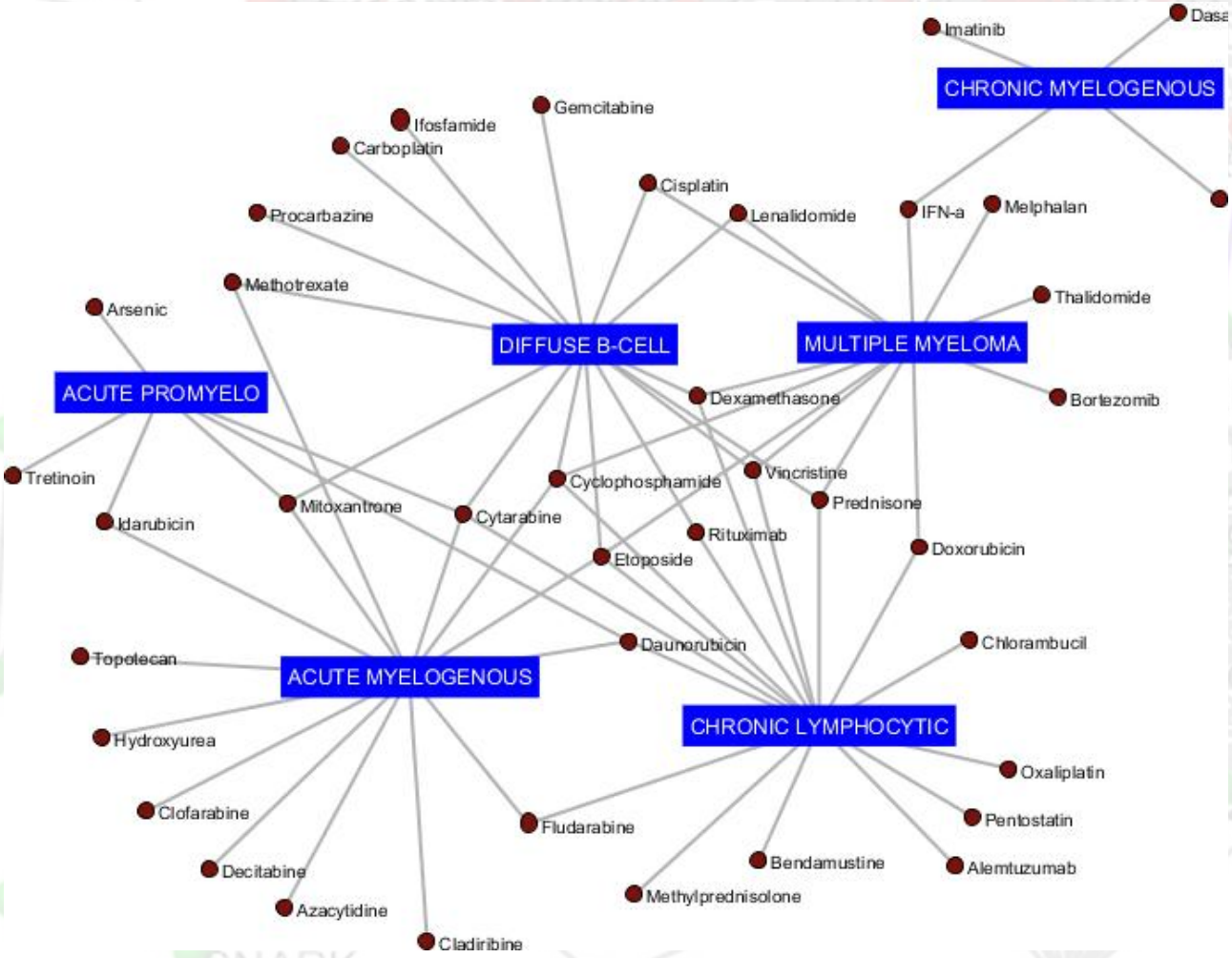
Atypical cancer therapy (leukemias/lymphomas)

- Chemo “lite”: Immunomodulators
  - Interferons (mimic natural body protein)
  - Not as hazardous
- Specific (“targeted”) class
  - MABs (biological proteins)
  - TKIs (very targeted small molecules – usually pills and expensive)

Network 1: Drug to cancer

- Drugs were linked to the cancers as per NCCN treatment recommendations
  - Bipartite
- If NCCN says drug X is involved in treatment of cancer Y, then an edge X-Y is made.
- Non-directional, unweighted

Network 1: Drug to cancer map

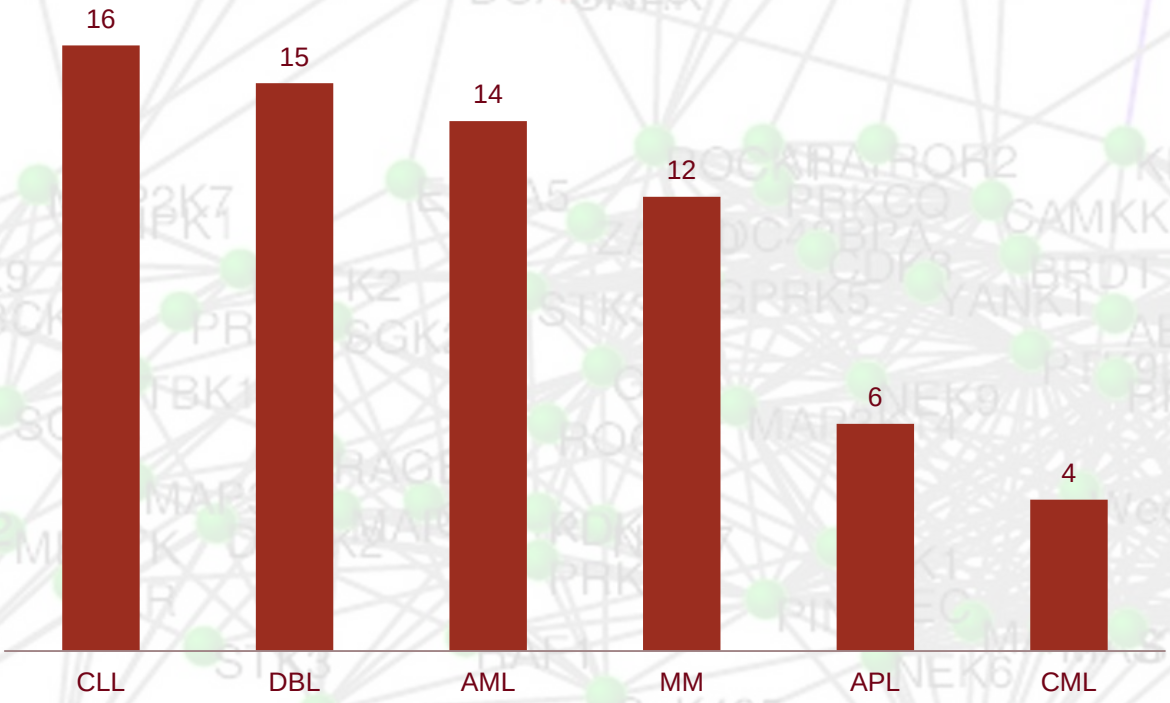


(Drawn with Network Workbench, Boerner et al., Indiana University Bloomington, Bloomington, IN 47405)

Network 1: Metrics

[All non-network graphs made with Microsoft Excel, Microsoft Corp., Redmond, WA]

# of drugs used in each cancer

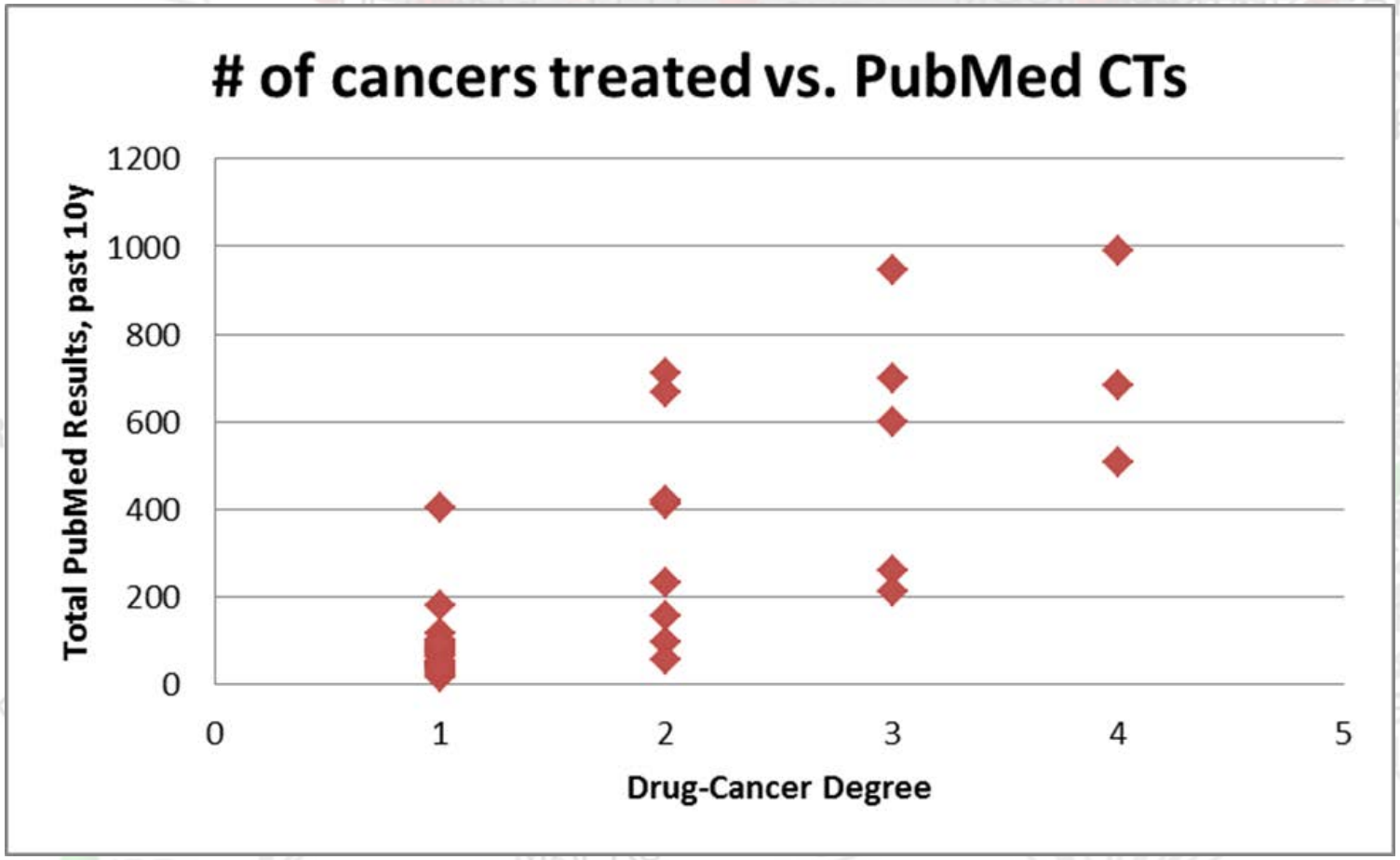


[Linear R-squared = 0.906]

Network 1: Metrics

Ranked "Histogram": Drug category vs. cancers treated

Network 1: Bibliometric Comparison



Network 1: Despair?

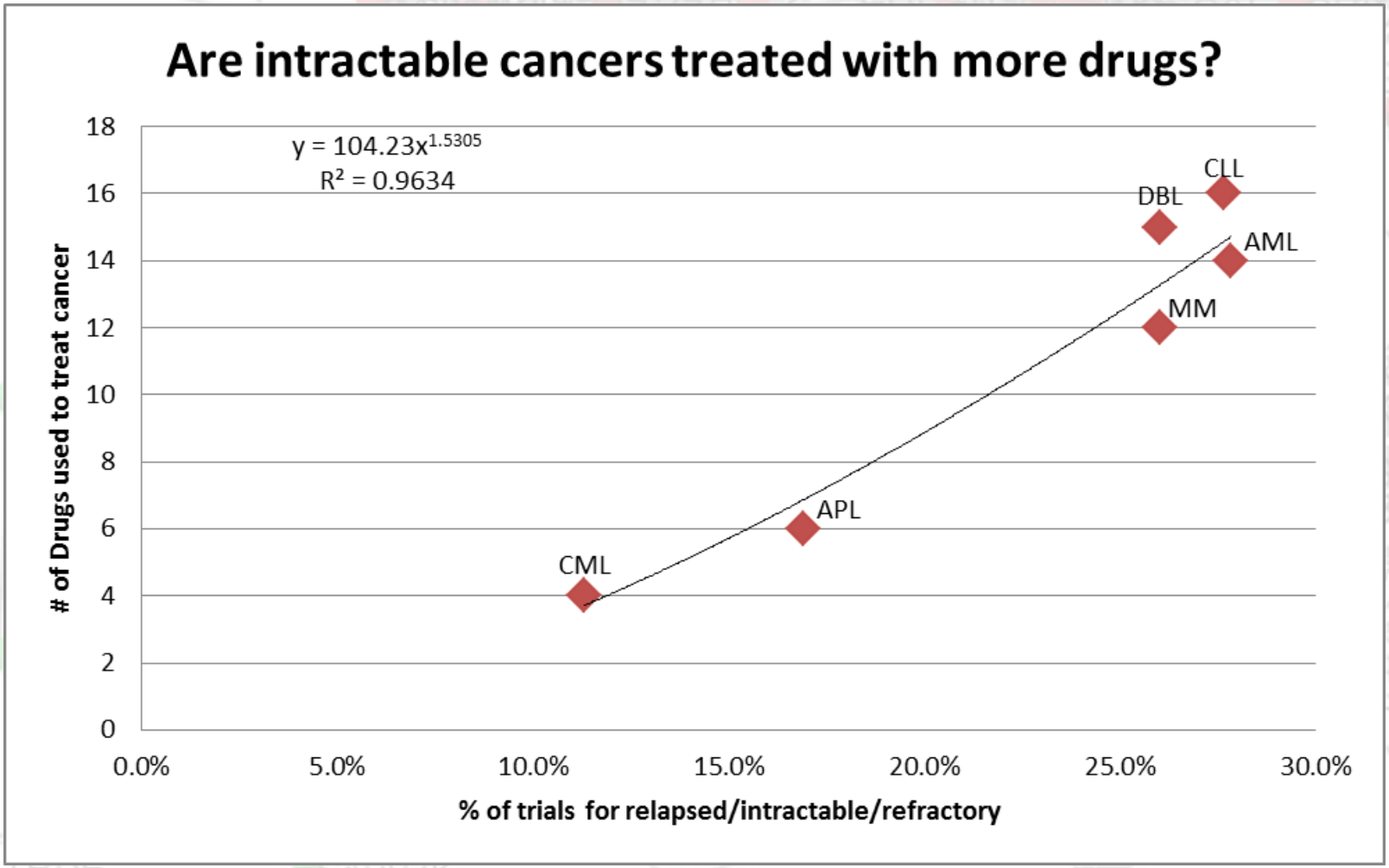
- Cancers that have high drug degree are difficult to treat [pers. comm.]
- Using degree metrics and data obtained from PubMed*, we impute “despair” for ea. cancer.
- Compare:
  - Mentions of cancer name with filter ‘clinical trial’
  - Vs. mentions of “[cancer name] AND (relaps* OR salvage OR intractable OR refractory) with filter ‘clinical trial’”
- Calculate % of mentions seeming “desperate” and plot against cancer-to-drug degree from network.
- More treatments required should = higher despair index.

* United States Government. “PubMed”. http;//www.pubmed.gov/

Network 1: Despair, quantified

Cancer	Total Mentions	# Refractory	% Refr.	Drug deg.
AML	909	253	27.8%	14
APL	136	23	16.9%	6
MM	1187	309	26.0%	12
CML	406	46	11.3%	4
CLL	423	117	27.7%	16
DBL	411	107	26.0%	15

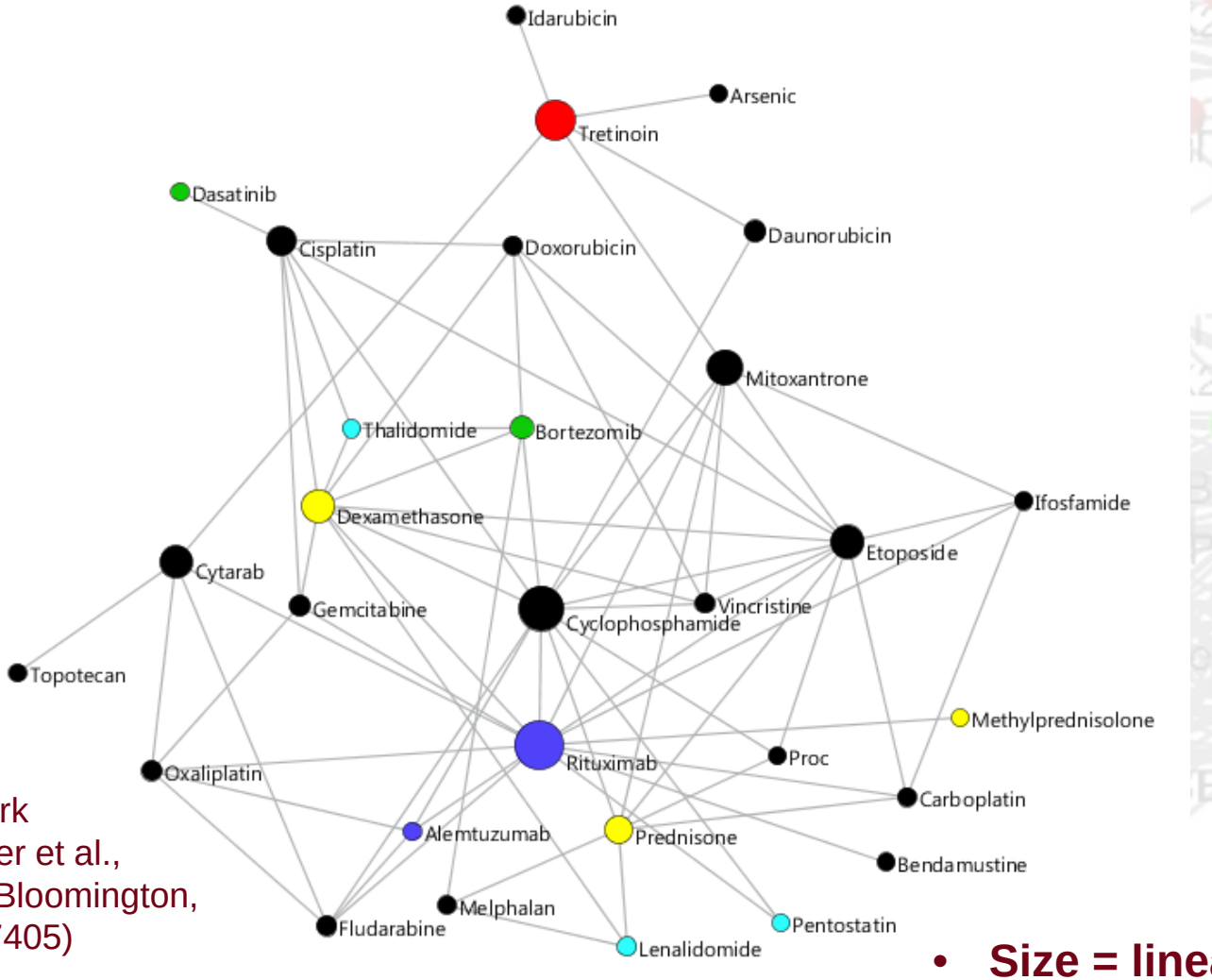
Network 1: Despair, plotted



Network 2: Cocktails

- I.e., regimens of multiple drugs used to treat cancers
- Drugs X, Y, and Z are connected as a clique IFF NCCN says they are used together in treatment of ANY cancer.
- Unipartite modeling (cancers ignored)
- Drugs linked to one another based on mention of co-therapy in NCCN guidelines, regardless of cancer.

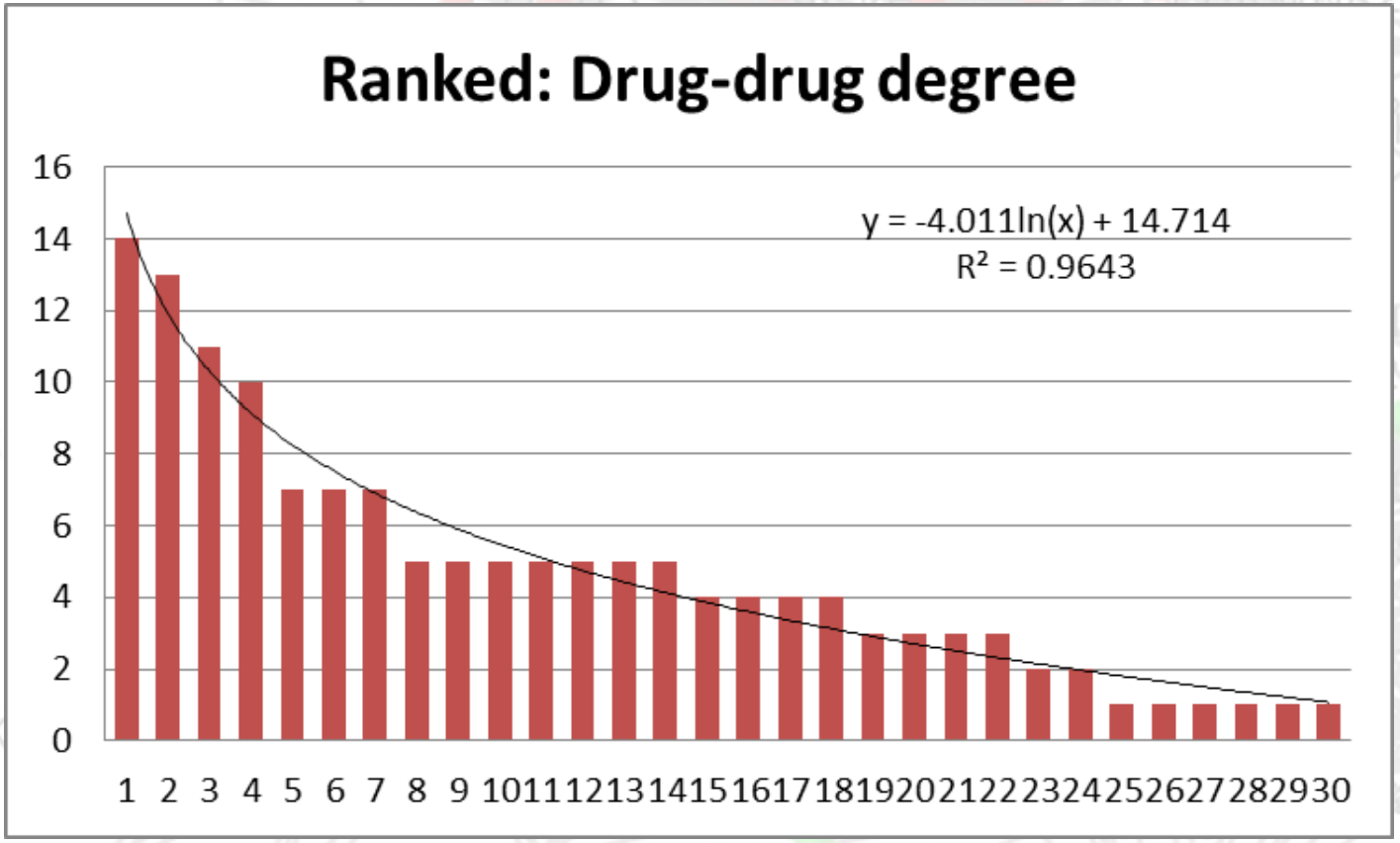
Network 2: Cocktail Map



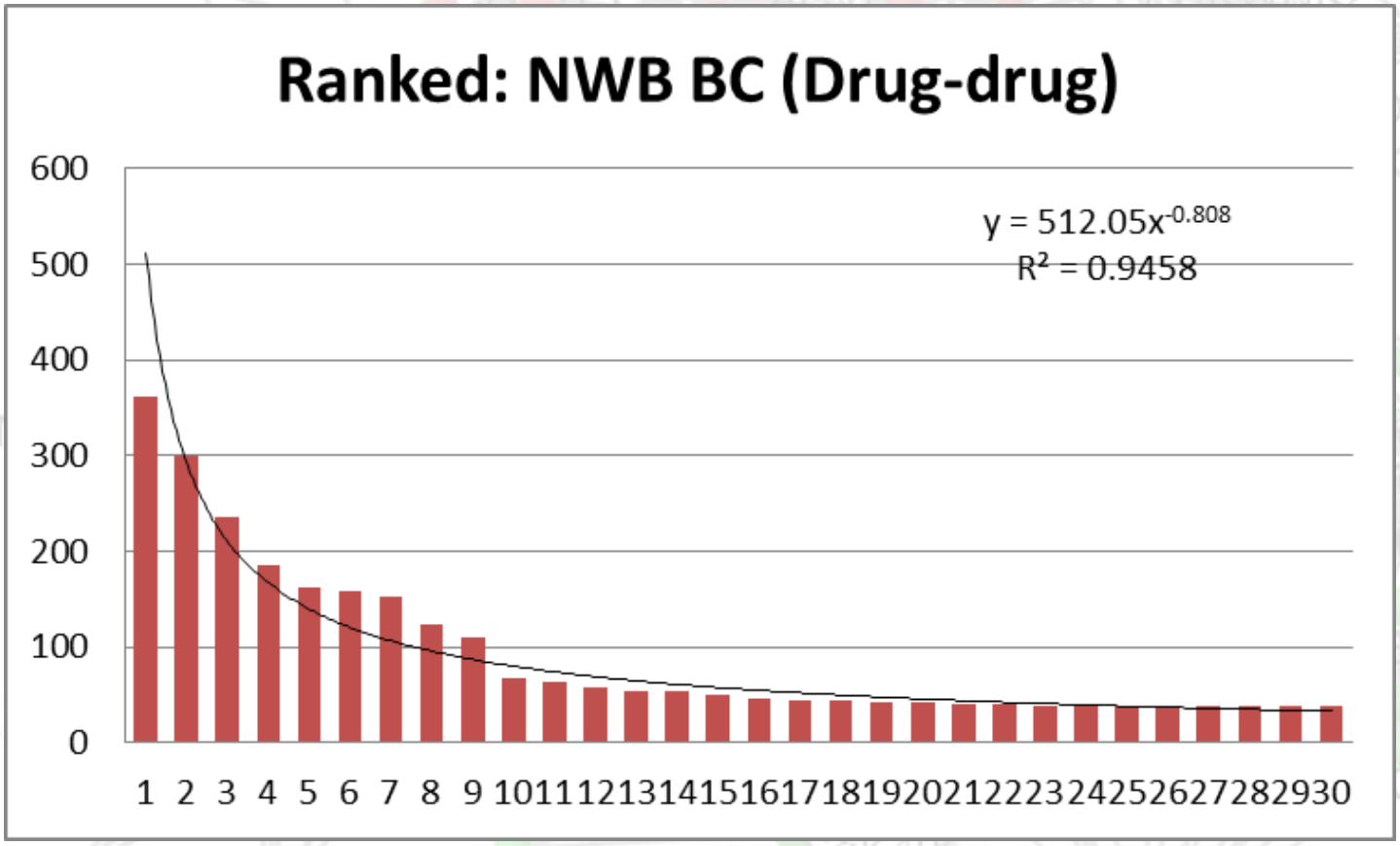
(Drawn with Network Workbench, Boerner et al., Indiana University Bloomington, Bloomington, IN 47405)

- **Size = linear to BC**
- **Color = category**

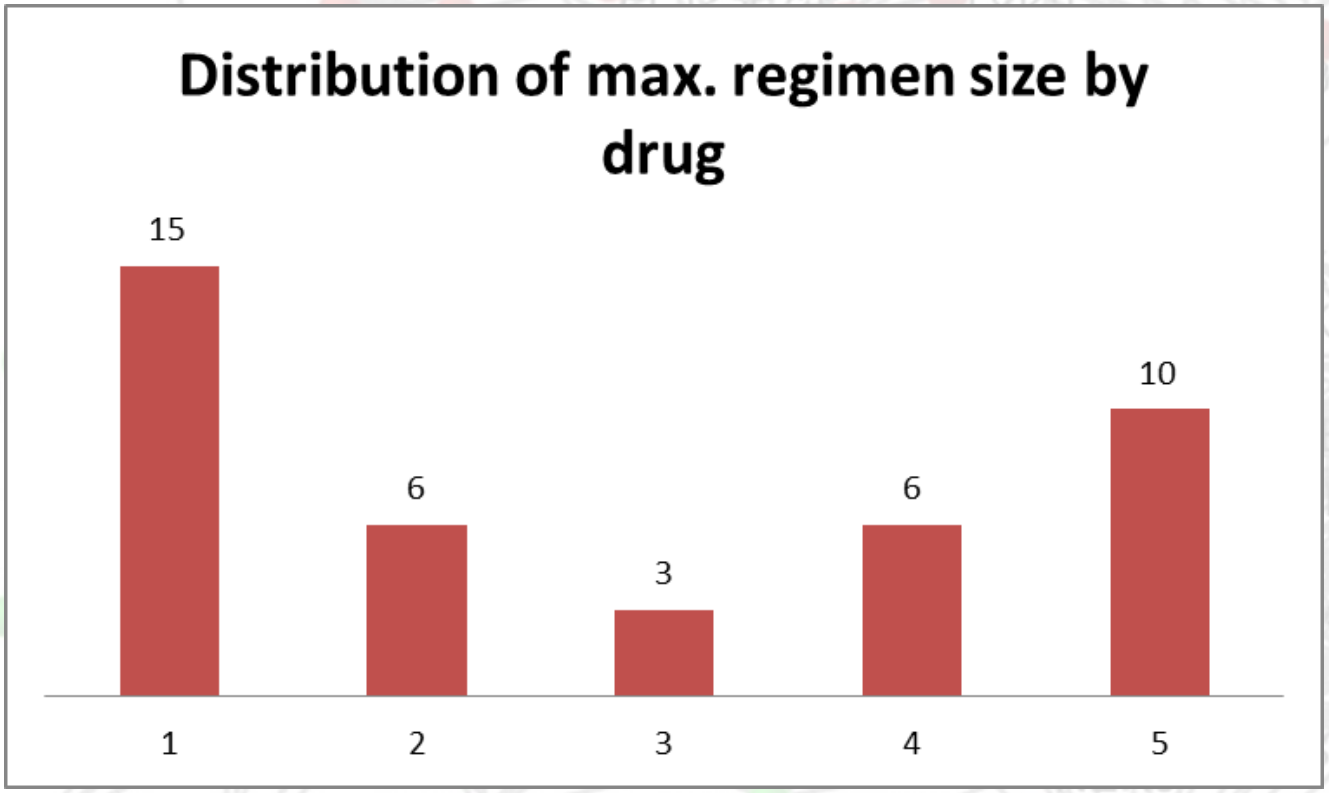
Network 2: Metrics



Network 2: Metrics

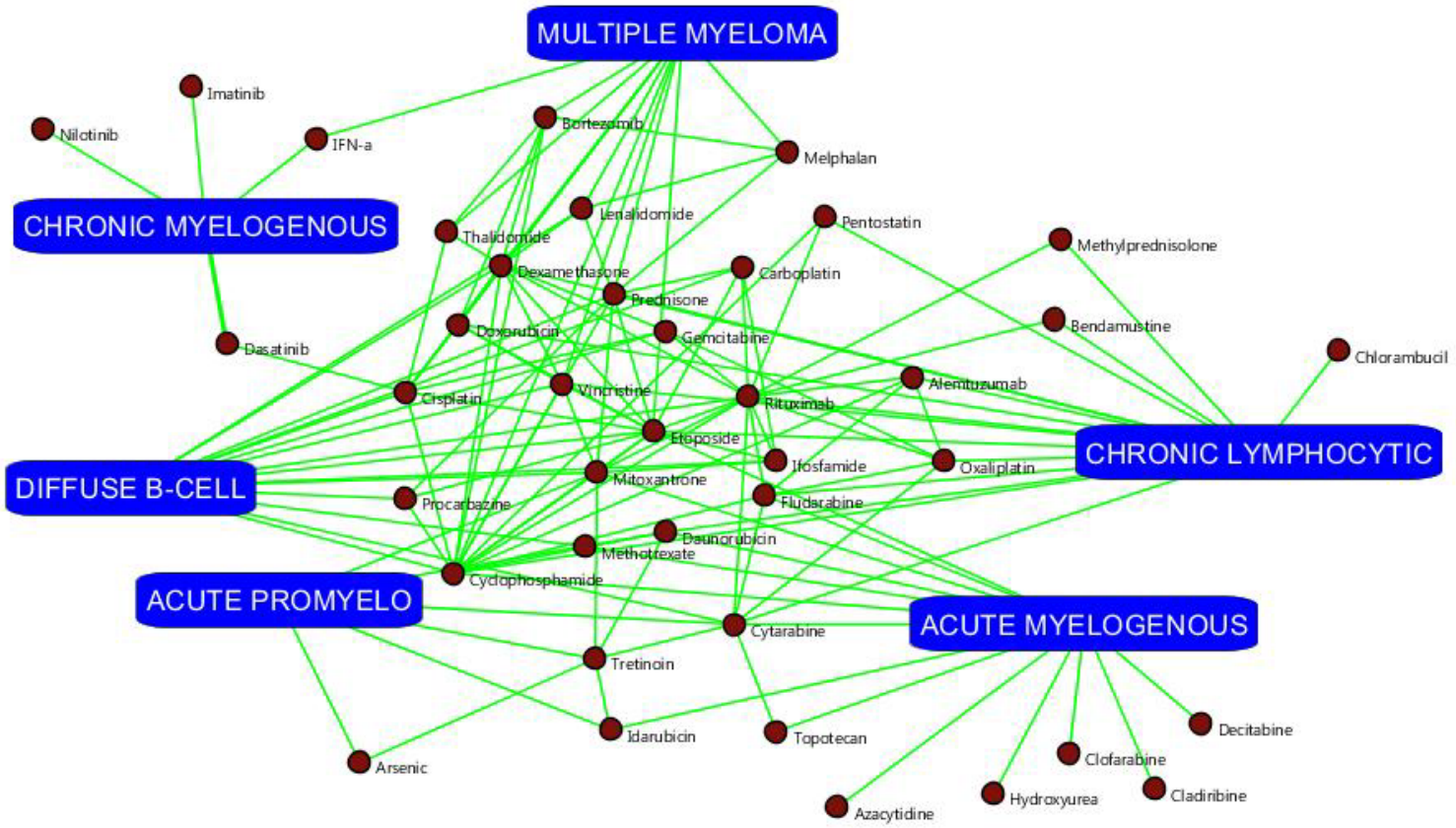


Network 2: Metrics



Regimen size = NWB K-core + 1

All together now!



[you can see why the entire drug-to-regimen bipartite graph visualization is not useful.]

Conclusions

- Ranked, degree distribution from drug to cancer is roughly linear (R-squared = 0.905), but low N again.
- Drugs that treat more cancers have more mentions in PubMed (low N though)

Conclusions

- Intractable/refractory/relapsed cancers tend towards higher degree in terms of number of drugs attempted (power, R-squared = 0.963). However, beware of low N.
- “You risk your life”: Older cytotoxics still connected to many cancers when drugs are grouped by class.
  - Preferential attachment? Difficult to prove.
  - Confirmation bias? Easier to prove.

Conclusions

- Max. regimen size a drug was involved in followed a U-shaped curve (i.e., many monotherapies and many large regimens, but few in between)
- Ranking of network distribution metrics (degree/BC) in the drug-drug network generally followed logarithmic or power distributions, though not necessarily those of power laws.

Conclusions

- Higher BC was seen in cytotoxic medications
  - = High Use and criticality to regimens; may form “basis” of regimens.
- High BC also seen in monoclonal antibodies (MABs) due to Rituximab.
- Caveat: These drugs are crucial *only in view of current treatment recommendations.*

Limitations

- Low N for cancers and drugs
  - Low treatment information freely available from NCCN
- Dependence upon NCCN
  - NCCN shows high bias and there is no absolute authority in oncology.
  - PubMed metadata (XML) is not ontologized to retrieve regimen-cancer data.
- Questionable PubMed information retrieval w/respect to intractable cancers.

Future Directions

- Addition of other cancers and their treatments to network
  - = higher N
- Full multipartite analysis
  - Why? Drugs belong to regimens belong to cancers
  - Weighted network analyses
  - Requires more computing power
- Shortest path analysis
  - Crucial to determining “how far” a drug is from a cancer.
  - Calculating all shortest paths [ij] unfeasible due to number of nodes (even for this network, would require 2000+ loops in algorithm)

Questions/Comments?