Innovating with Existing Drugs and Nutraceuticals

Opening Remarks

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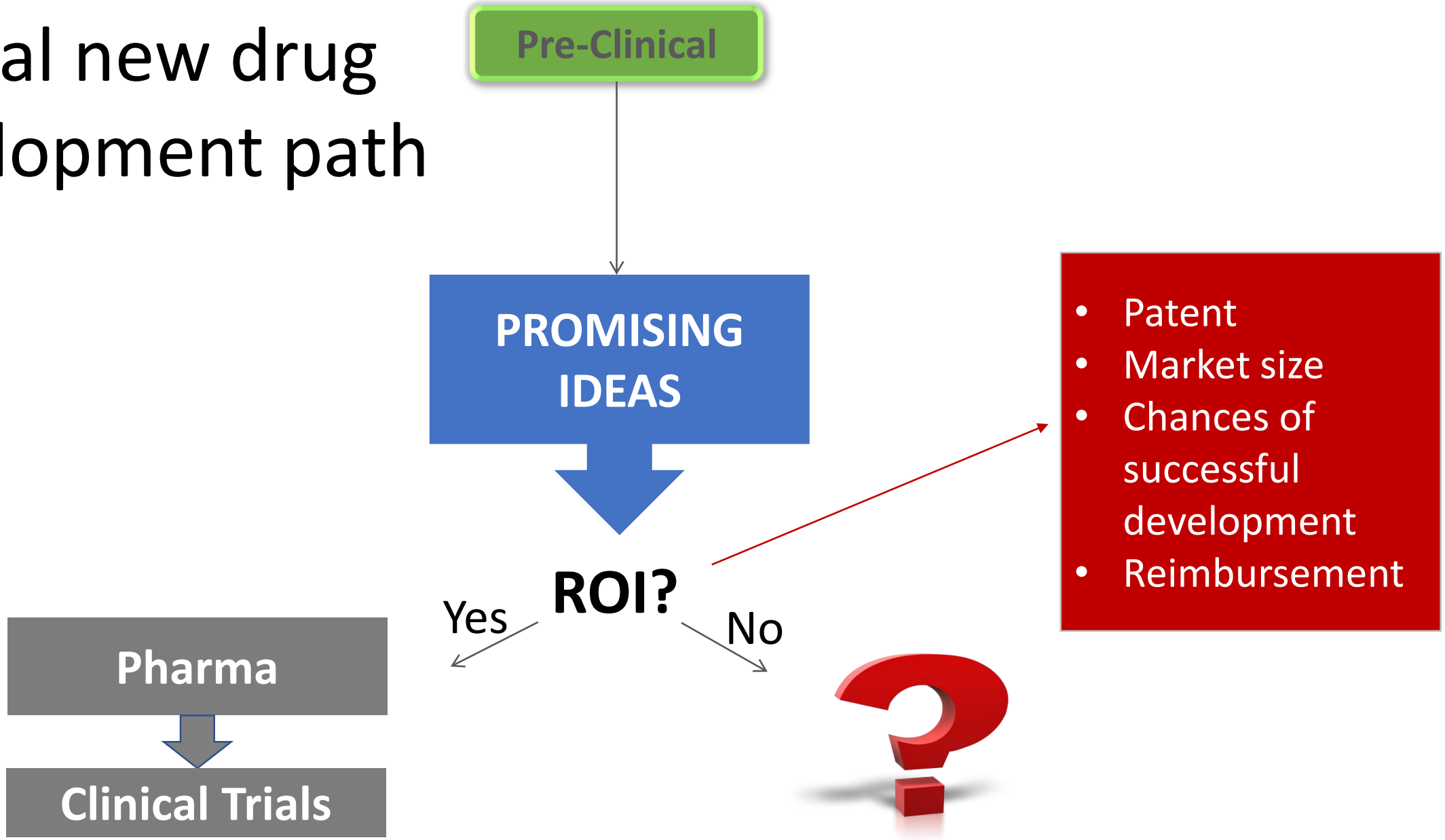
Problem and the Opportunity

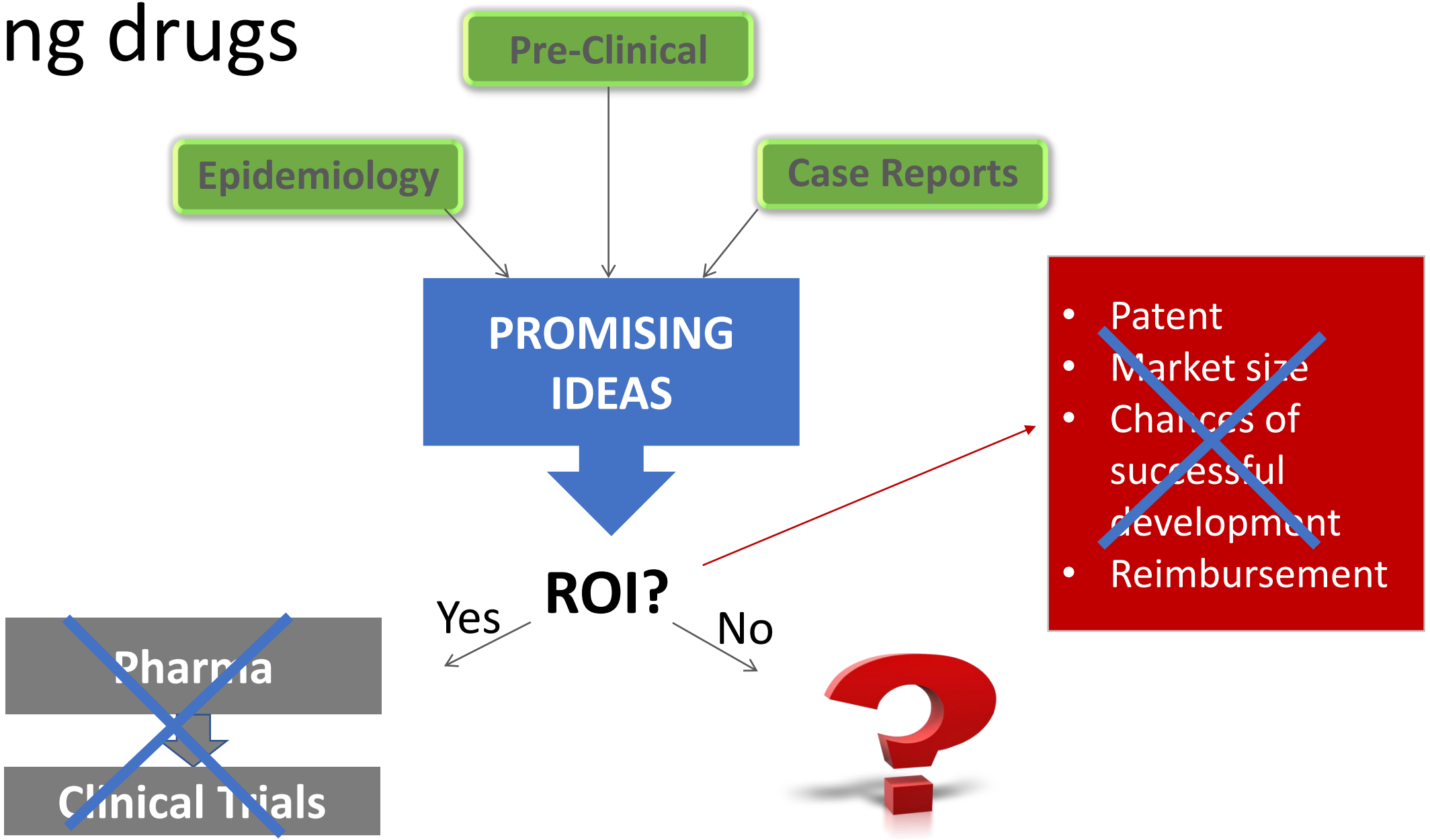
- Problem: There remain large unmet needs in medicine, since many therapies are expensive, quite toxic, or only modestly effective

- 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



Existing drugs



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

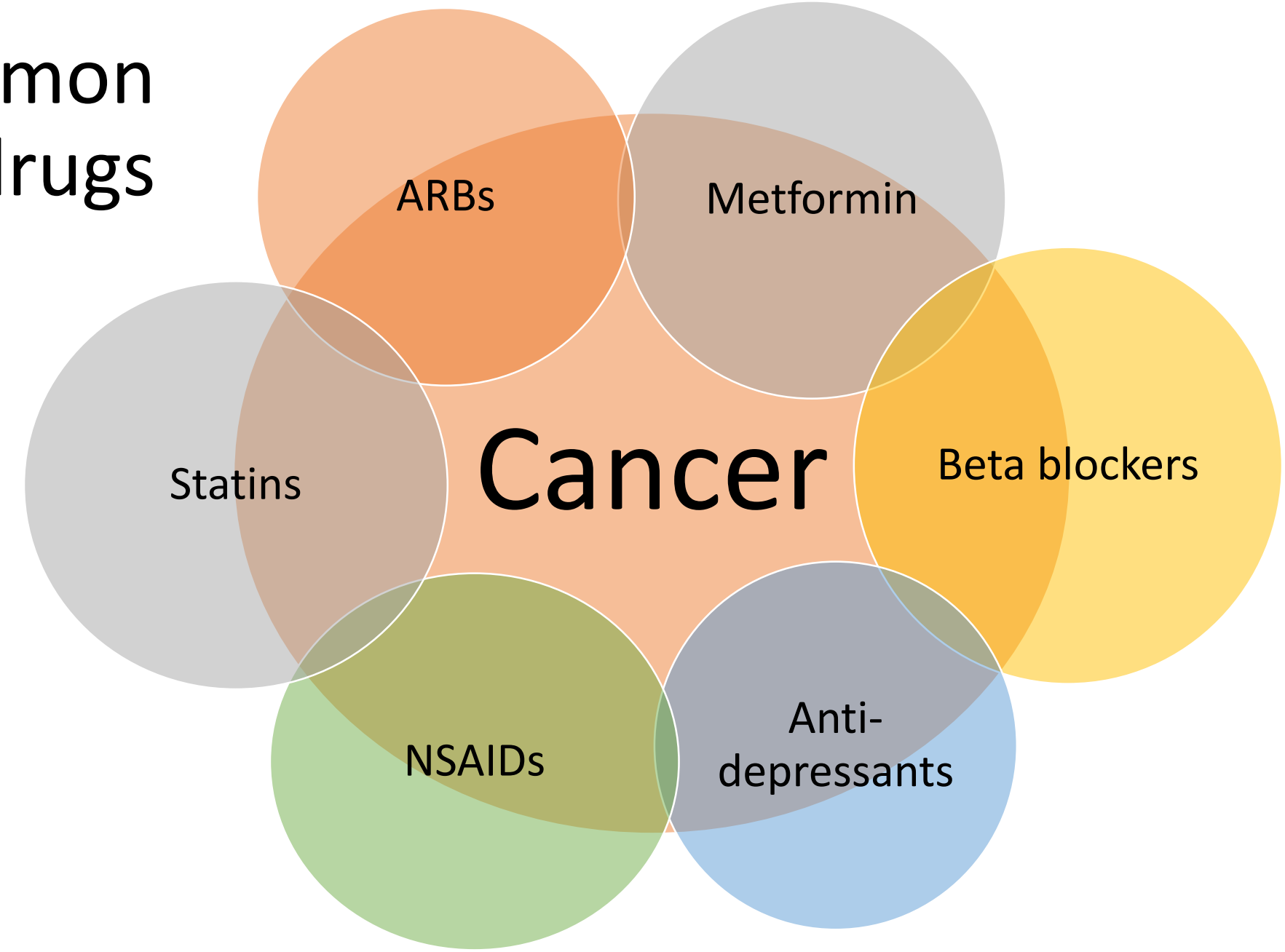
Challenges

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

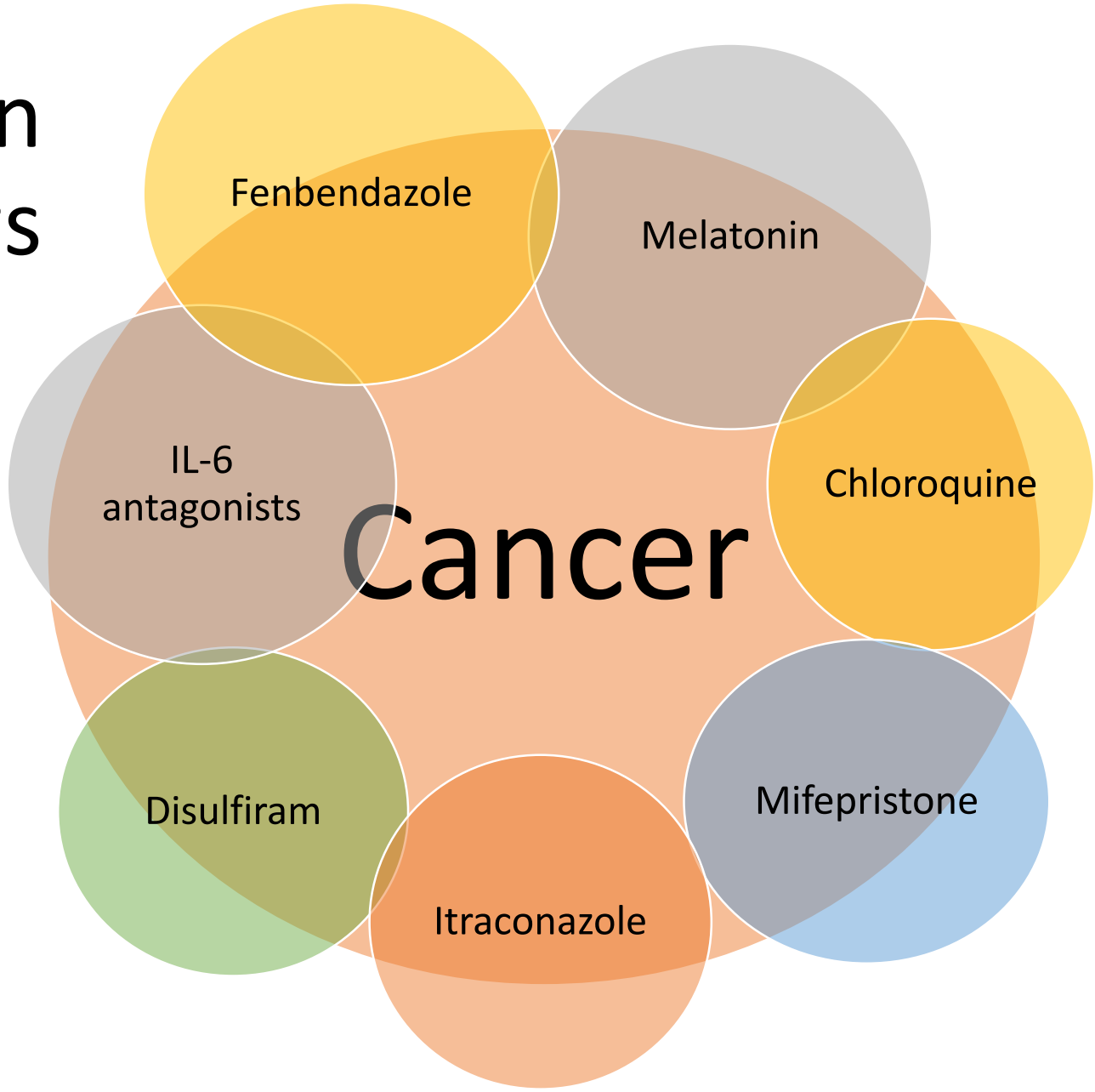
	Non-cancer drugs		Cancer drugs
	Common drugs	Uncommon drugs	
Epidemiology studies	X		
Pre-clinical research: in silico/wet lab	X	X	X
Case reports/ limited clinical trials		X	X

Interventions and prioritization

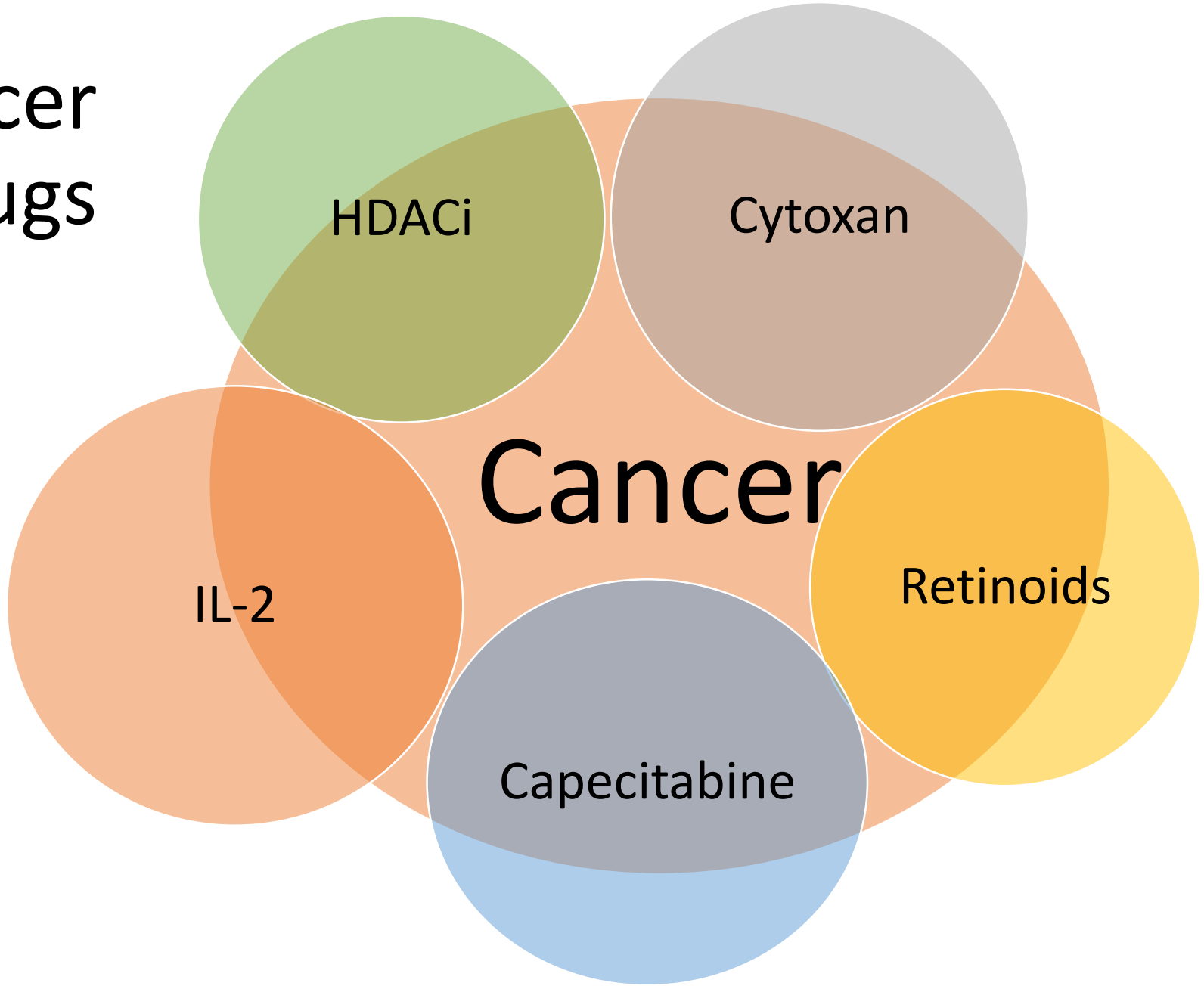
Common drugs



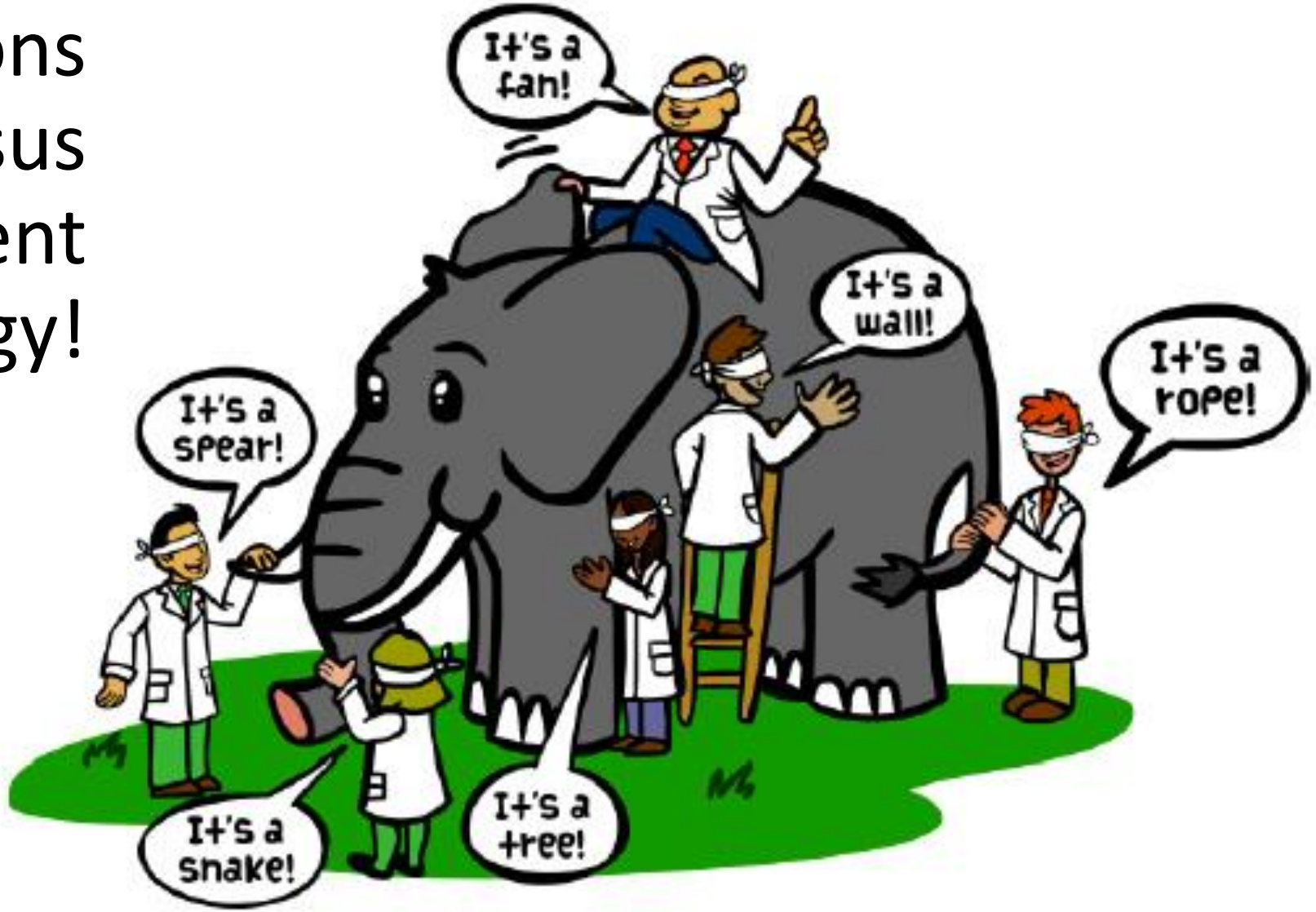
Uncommon drugs



Cancer drugs

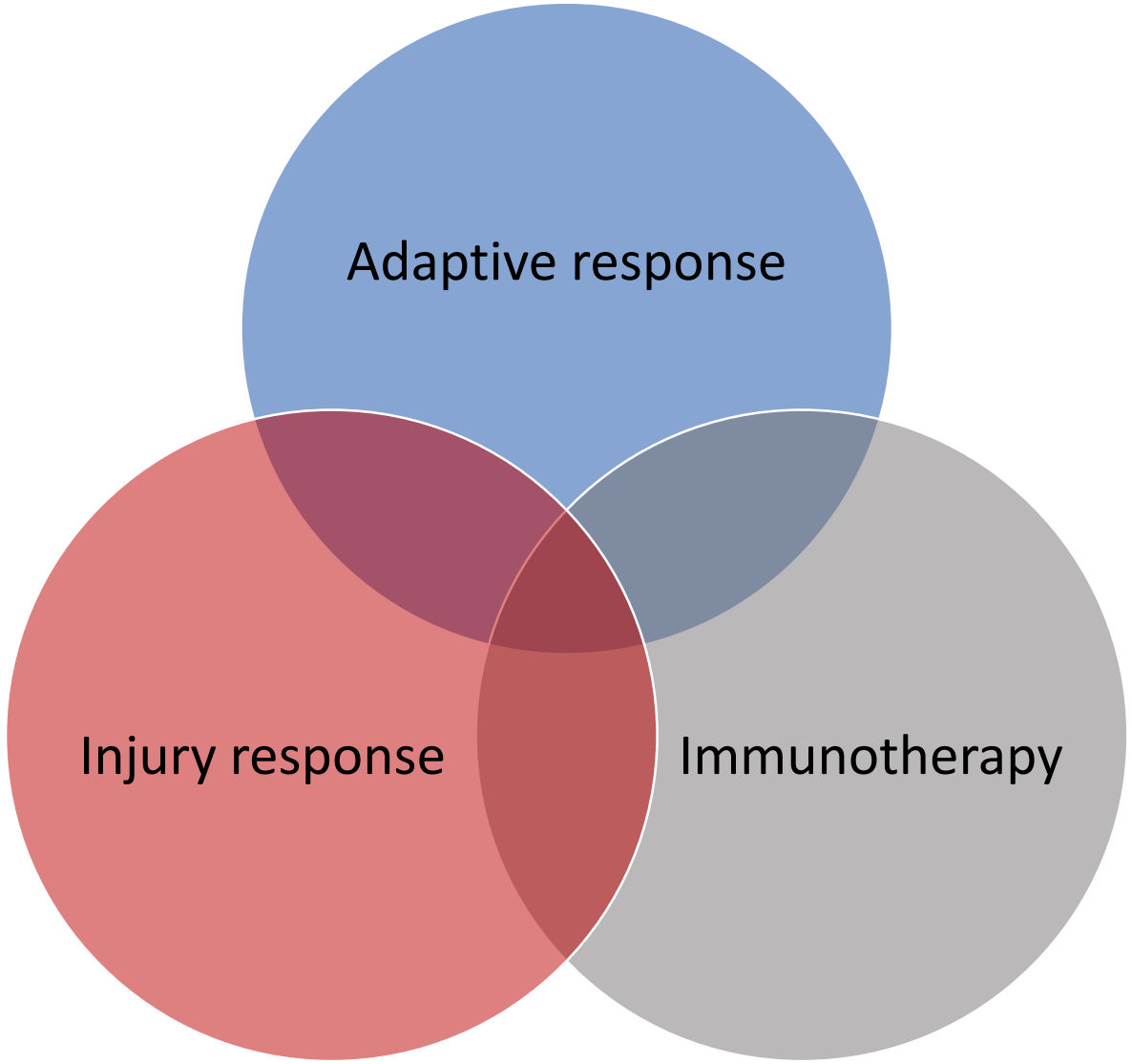


Too many options and no consensus on treatment strategy!

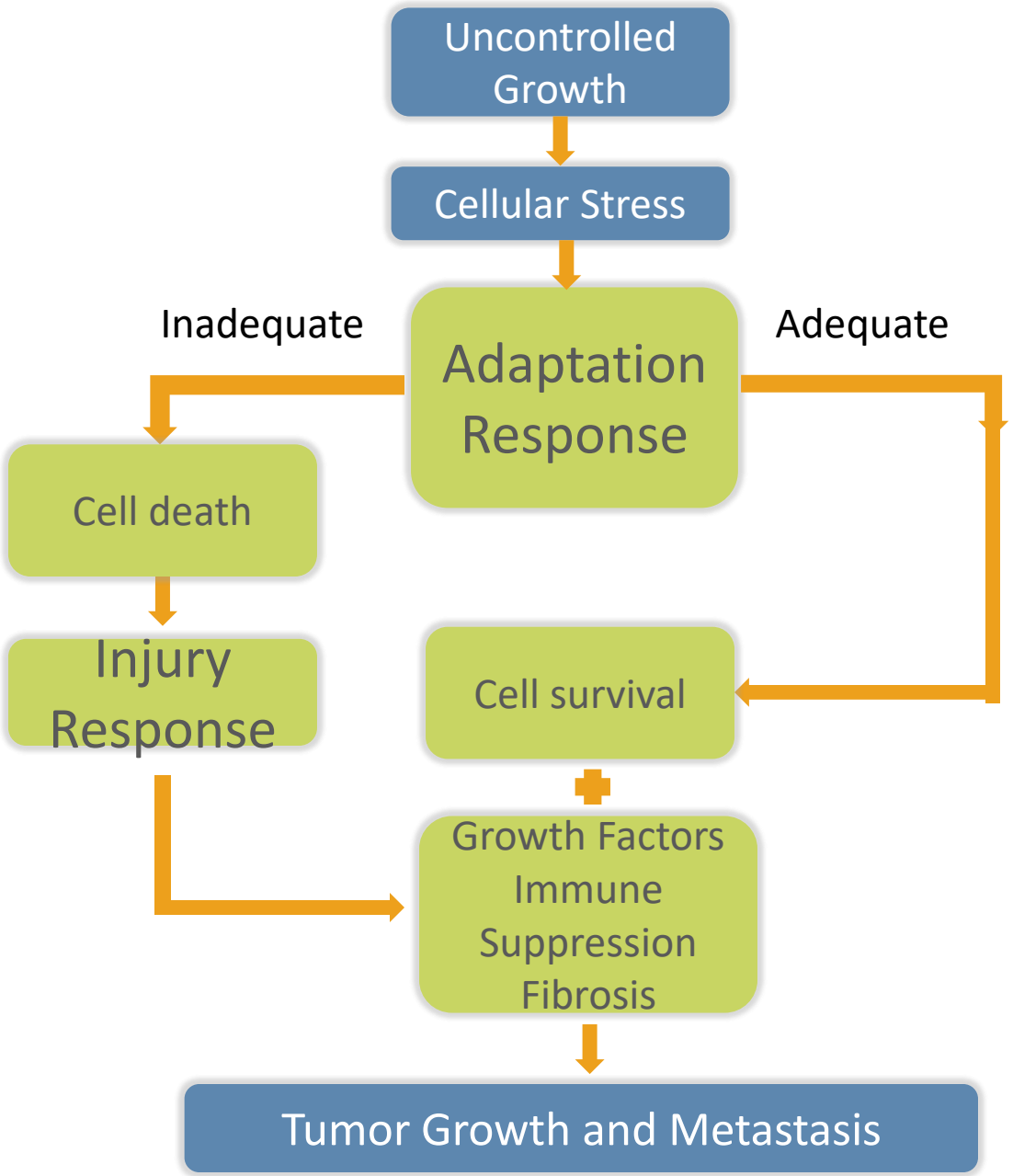


Scientific framework for prioritizing ideas

(for cancer)

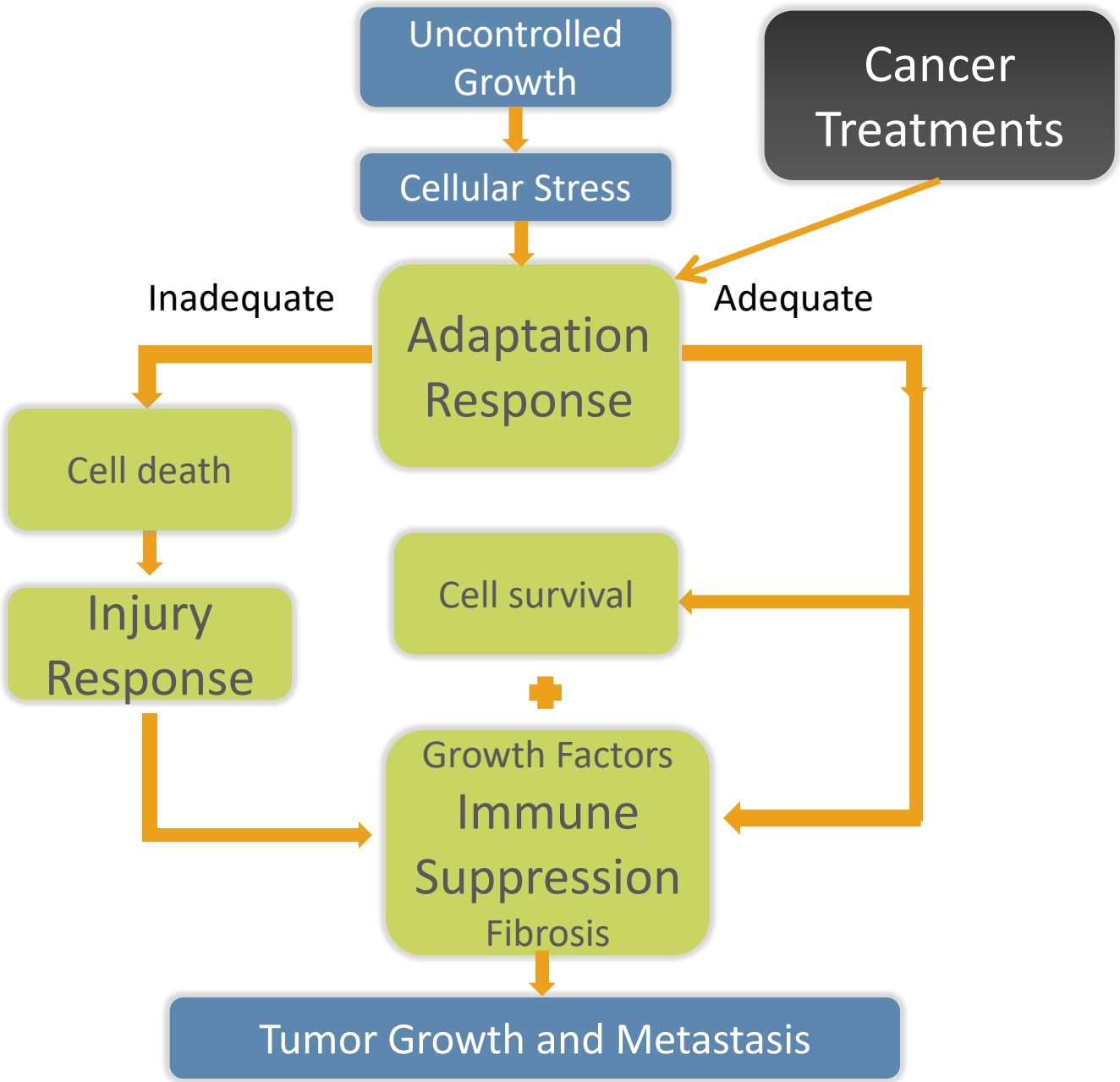


Scientific Framework



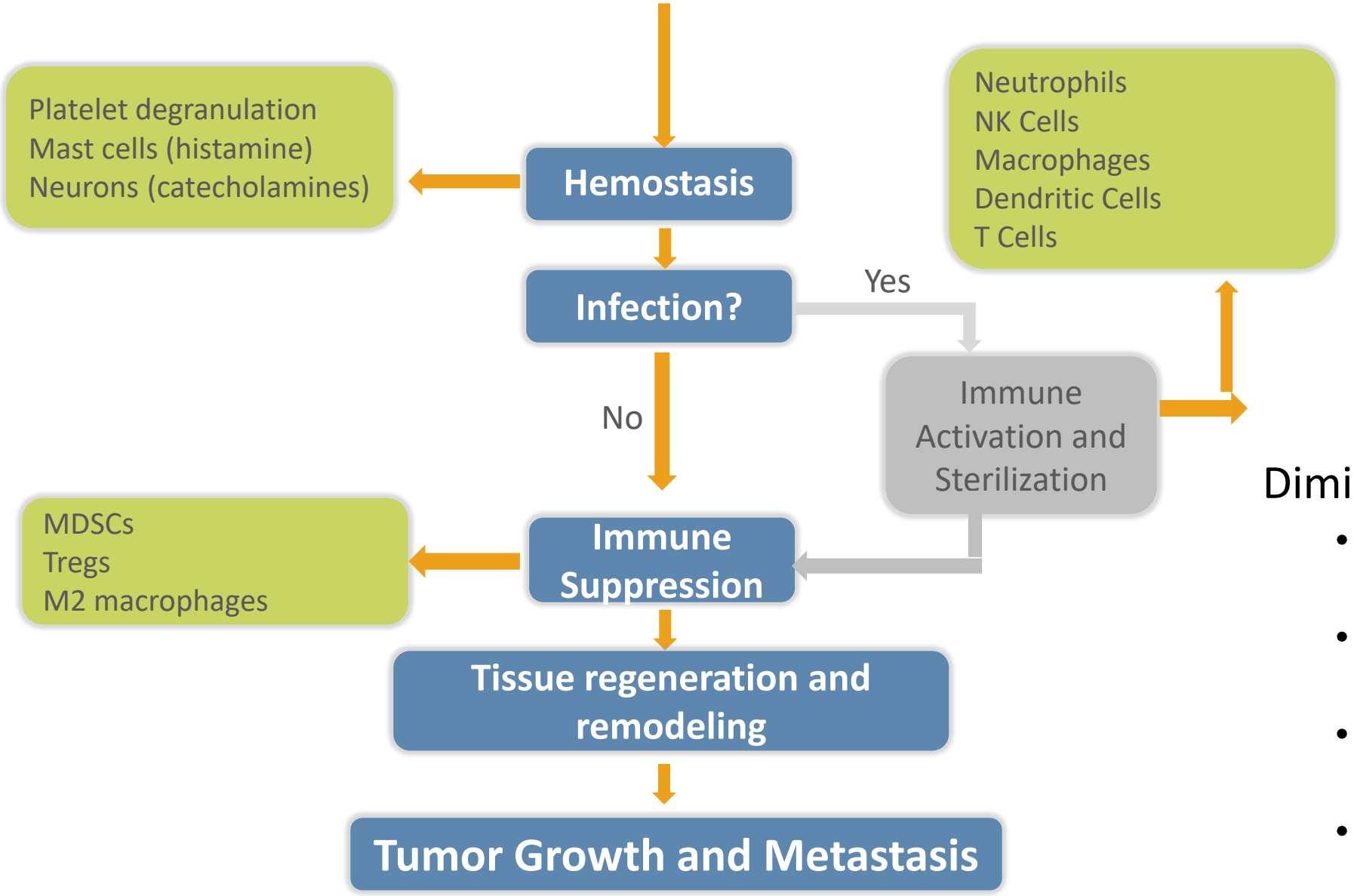
- Mutations give tumor cells a growth advantage over non-tumor cells
- Adaptation response leads to treatment resistance and cell survival
- Injury response leads to growth enhancing micro-environment and can awaken dormant mets
- Tumor cells are fertilized by the injury response and replenish injured tissue and provide a microenvironment conducive to tumor proliferation and spread

Scientific Framework



- Mutations give tumor cells a growth advantage over non-tumor cells
- Adaptation response can lead treatment resistance and cell survival
- Injury response leads to growth enhancing micro-environment 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



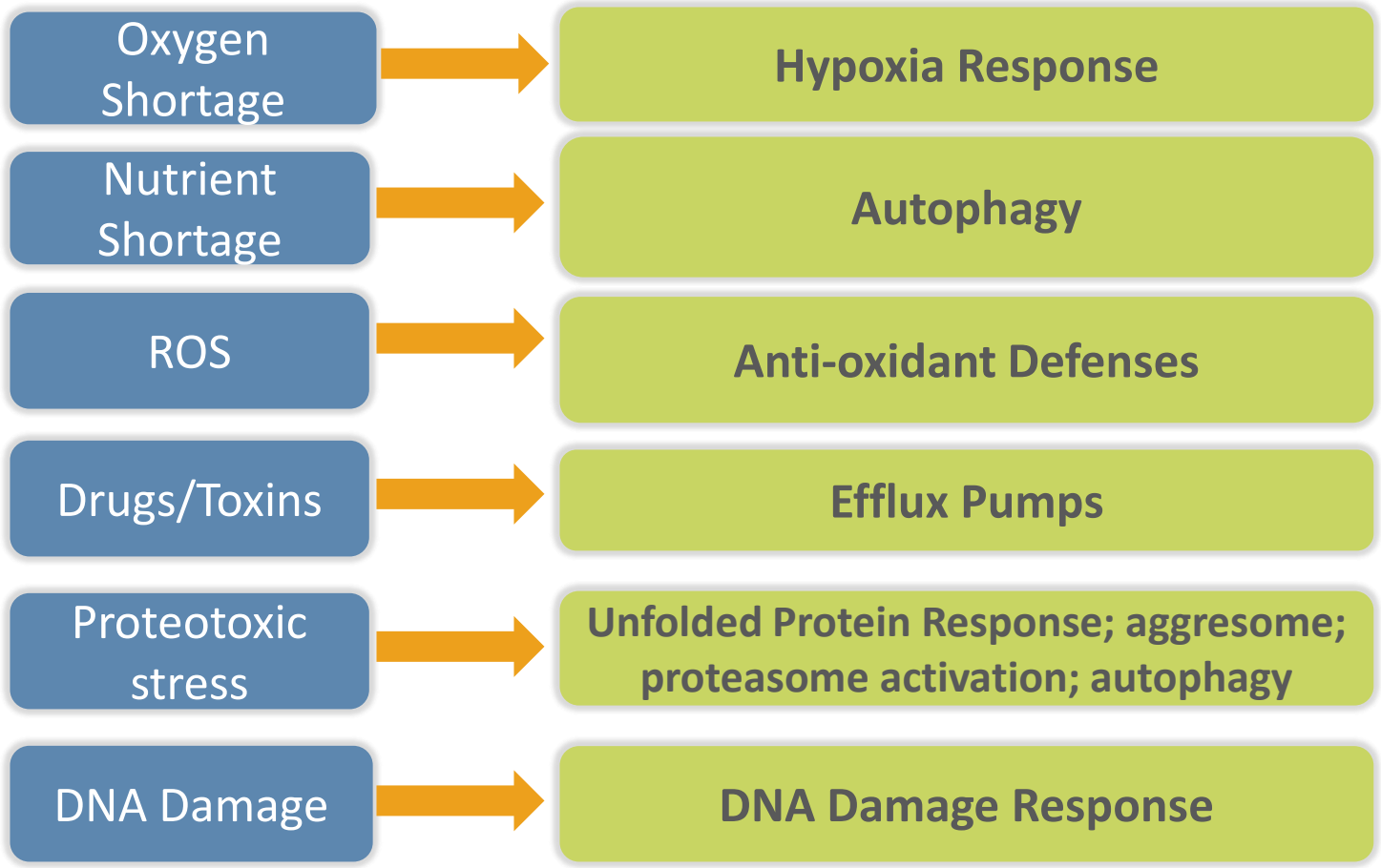
Diminish injury response

- Reduce chemokines, growth factors
- Mitigate immune suppression
- Stop epithelial to mesenchymal transition
- Reduce stem cell population

Blocking the Injury Response

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

Adaptive Response



Key immunotherapy steps

Initiate immune response to tumor

Reverse tumor induced immunosuppression

Localize effector response to tumor

Maintain effector response

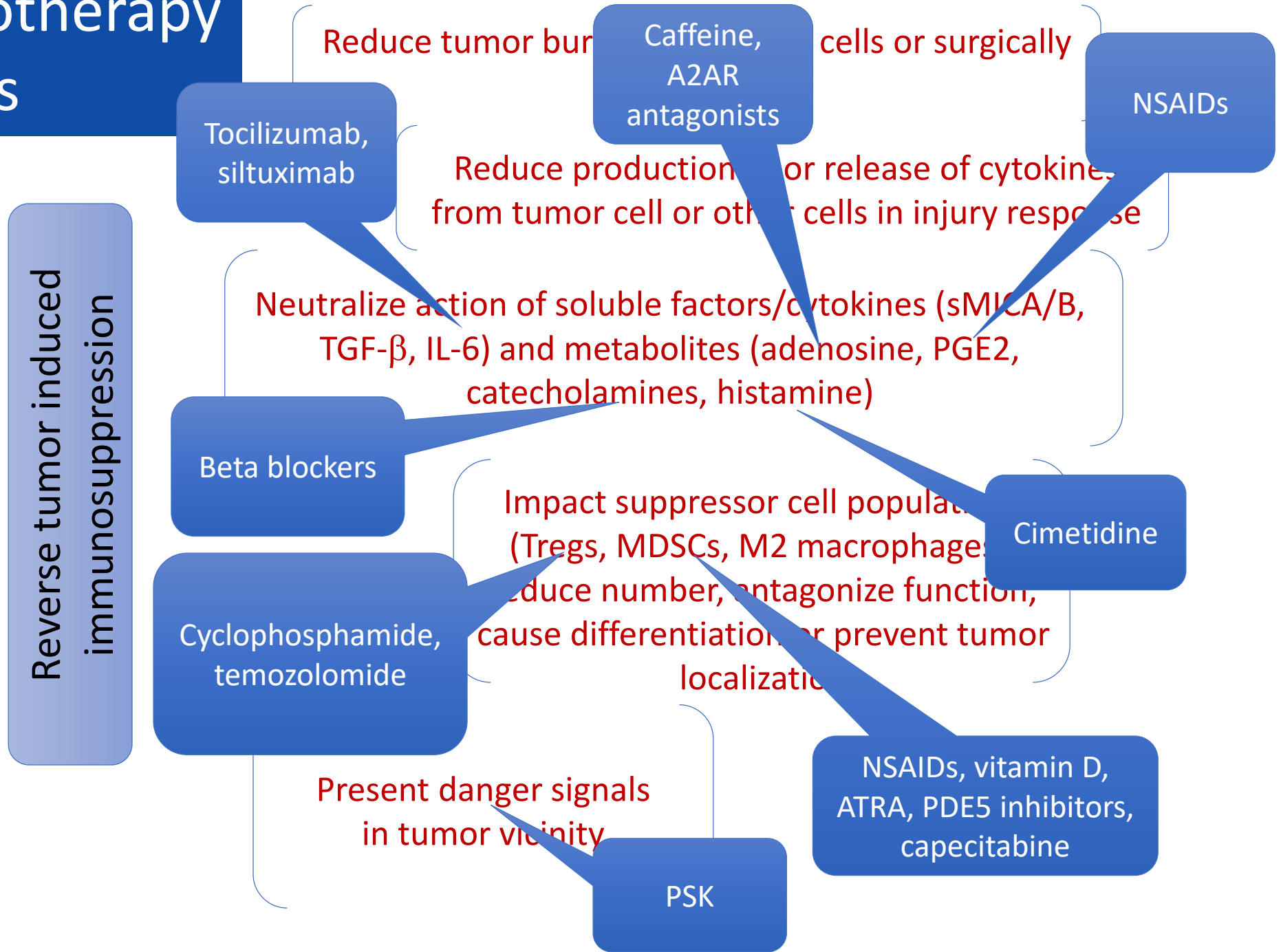
Create memory

Key immunotherapy steps

Reverse tumor induced immunosuppression

- 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

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

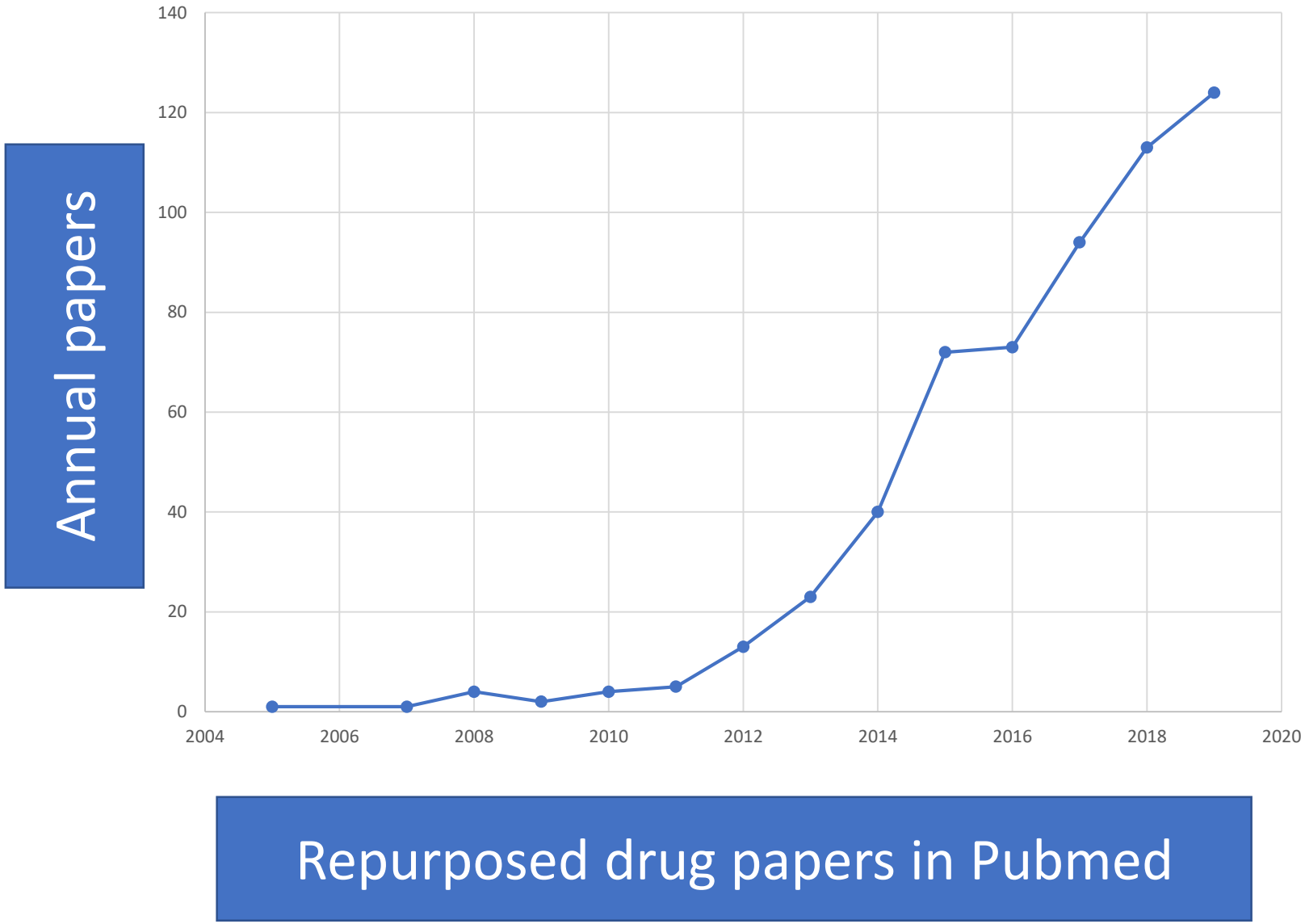
- Competition with pharma sponsored studies
- General disbelief
- Lack of awareness
- Pre-clinical and limited clinical data not strong enough to warrant further study
- Mechanism for cancer action may be not optimized

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



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

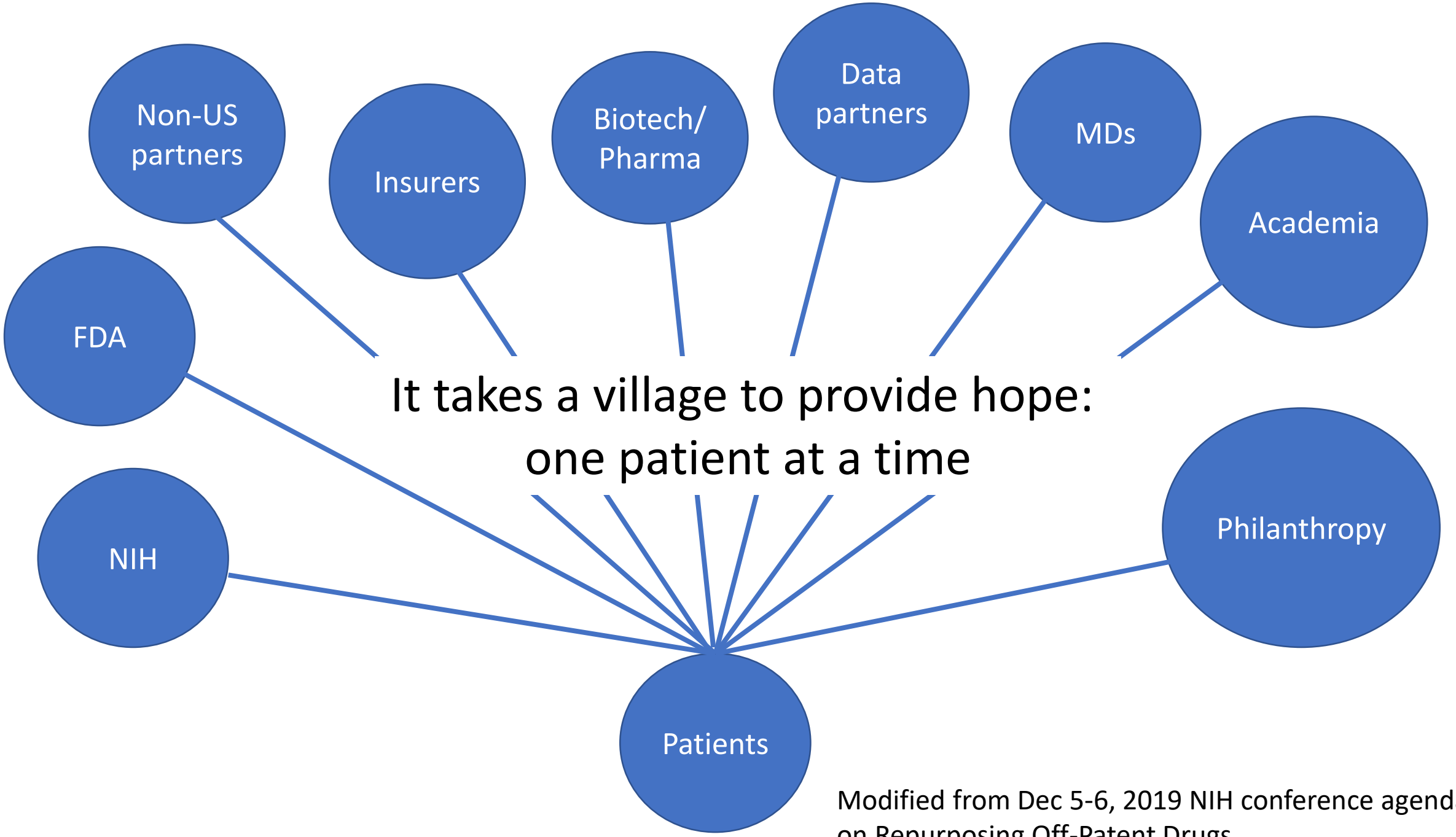
NOTE: In both cases, central site has IRB approval for study and may conduct safety and feasibility study prior to overseeing a distributed study in the community.

Advantages:

- Real world data
- Cost-effective
- High throughput

Challenges (perspective of patient, physician, institution):

- Medico-legal
- Ethical
- Business: who pays; incentivizing community MDs



Modified from Dec 5-6, 2019 NIH conference agenda on Repurposing Off-Patent Drugs

Desired outcome

Government commits $1 billion annually for 10 years to clear backlog of financial orphan opportunities