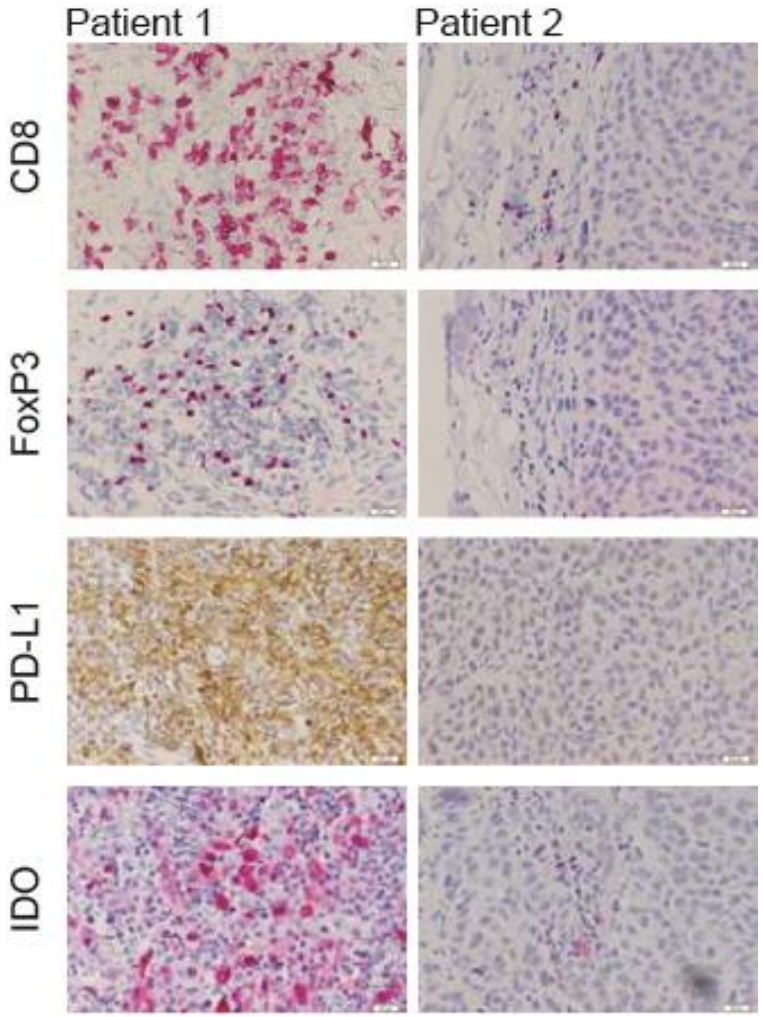
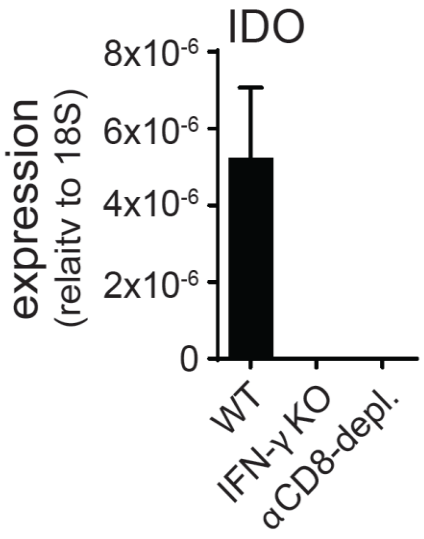
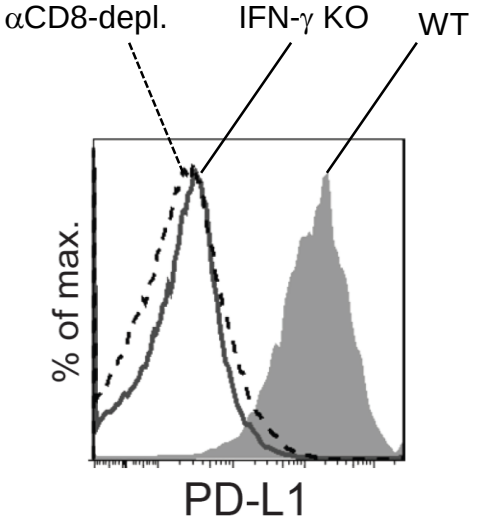
Transcriptional Patterns of Distinct Immune Landscapes

$CD8^+$ T cell inflammation is associated with an increased response to checkpoint blockade therapy



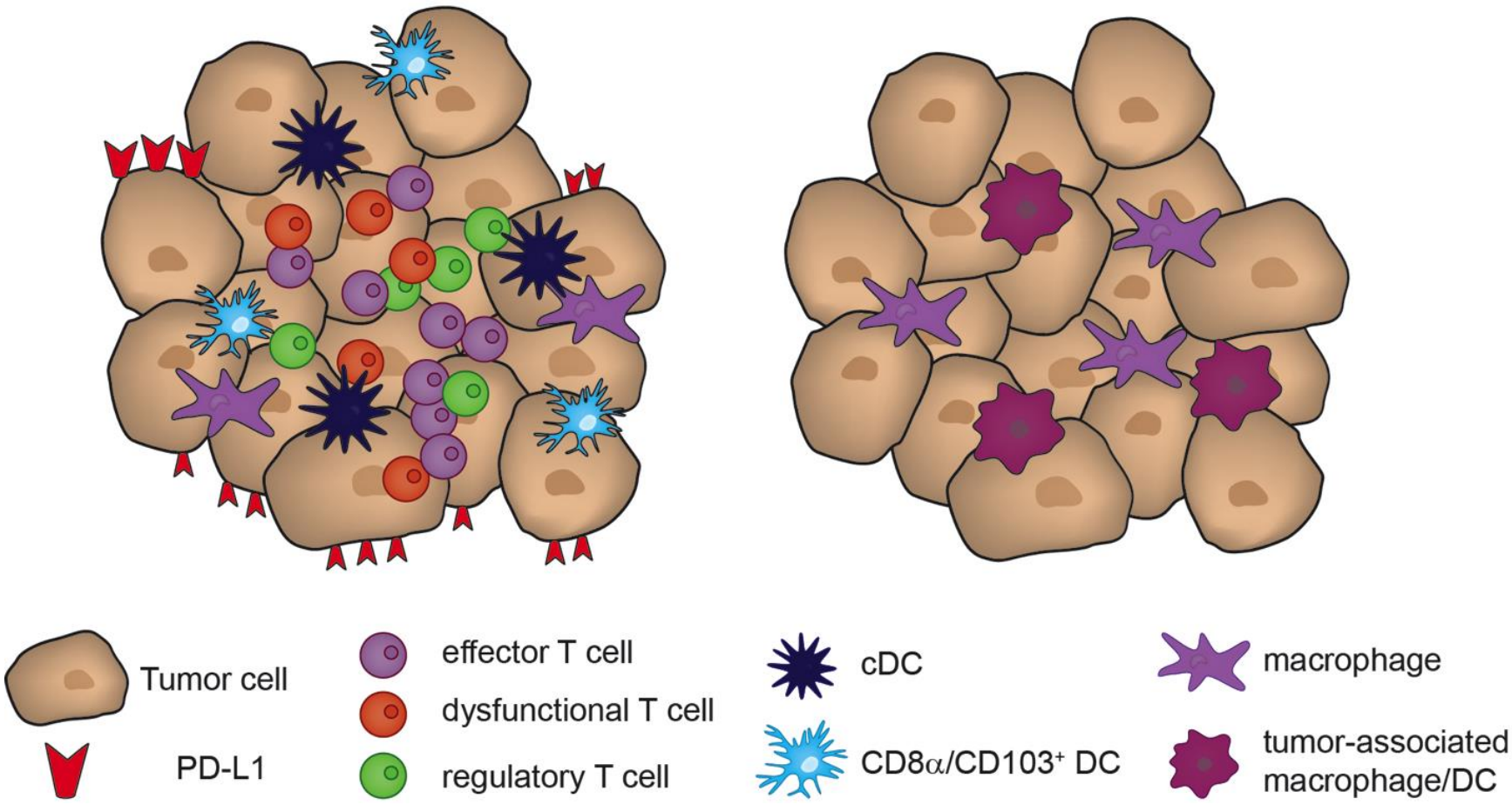


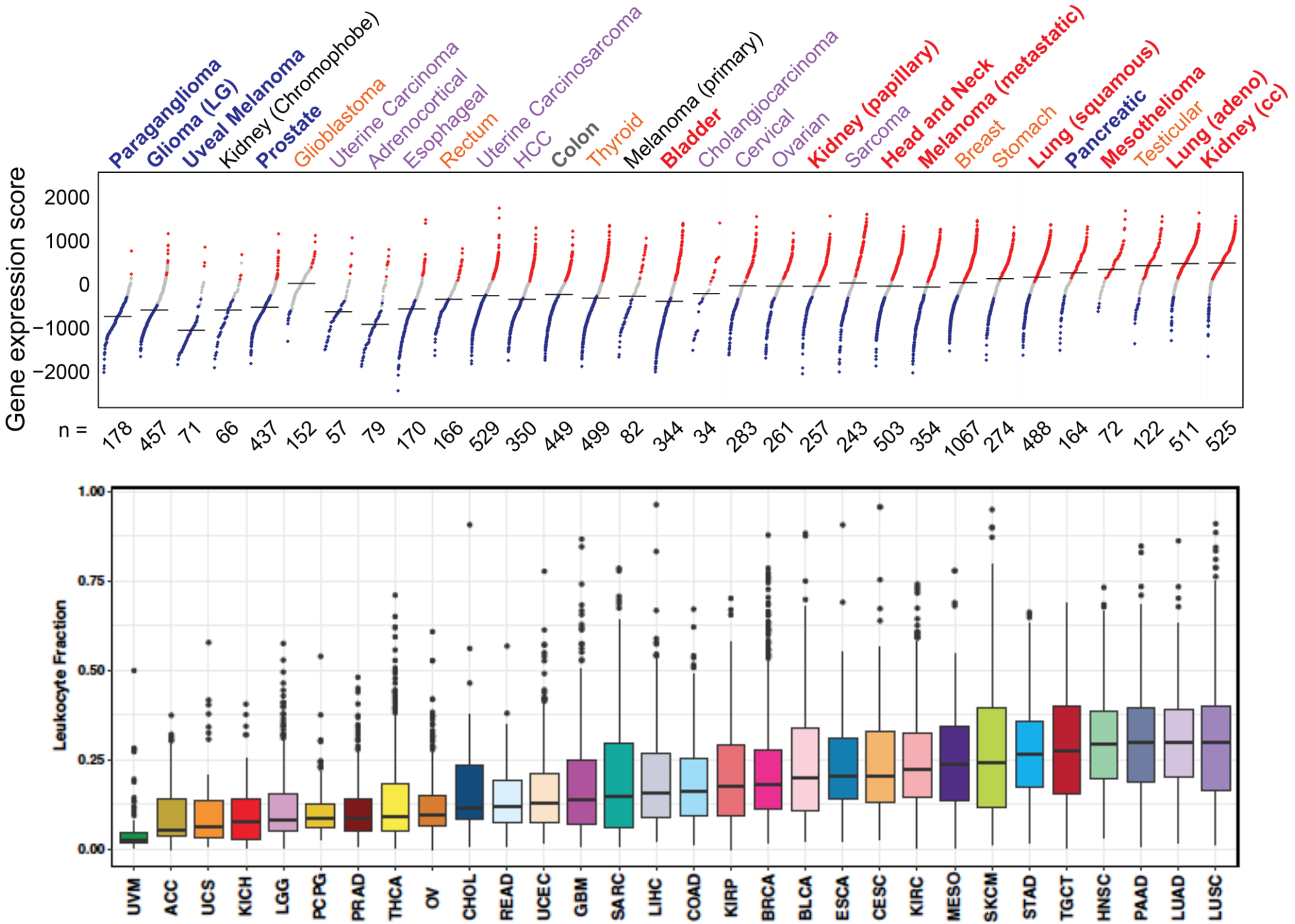


Spranger et al., STM 2013

T cell-inflamed Tumor

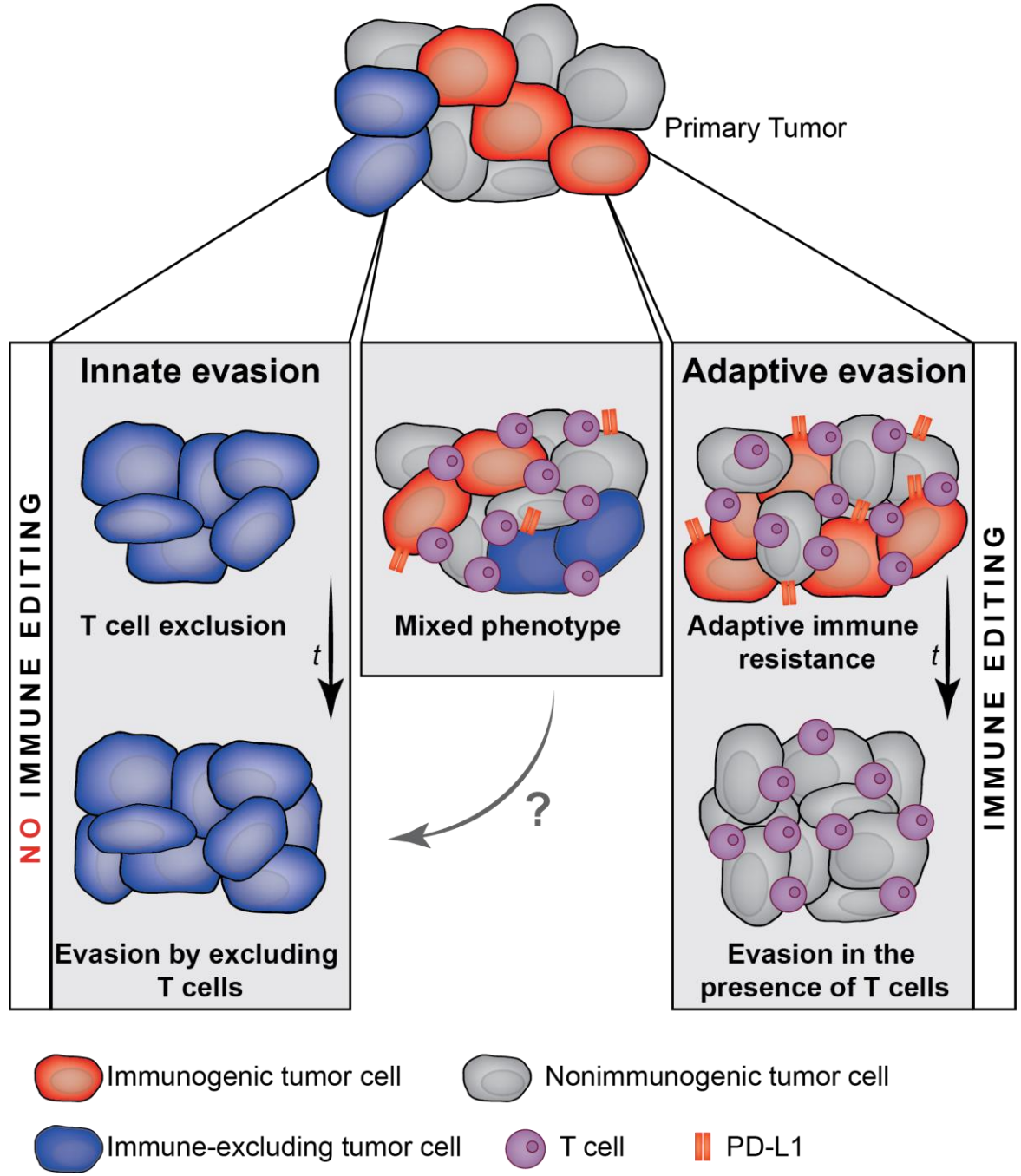
Non-T cell-inflamed Tumor



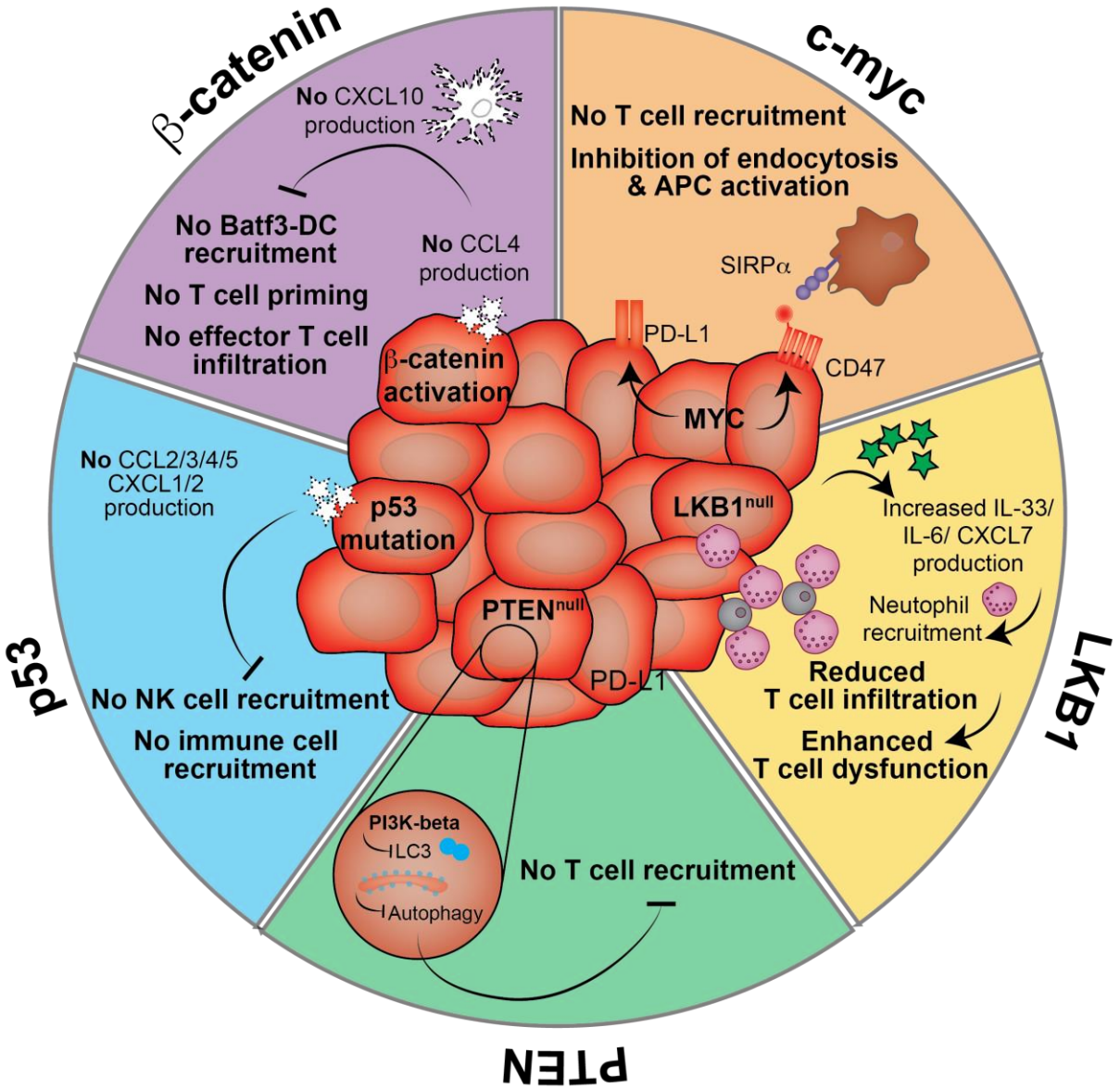


- **T cell-inflamed**
- **non-T cell-inflamed**

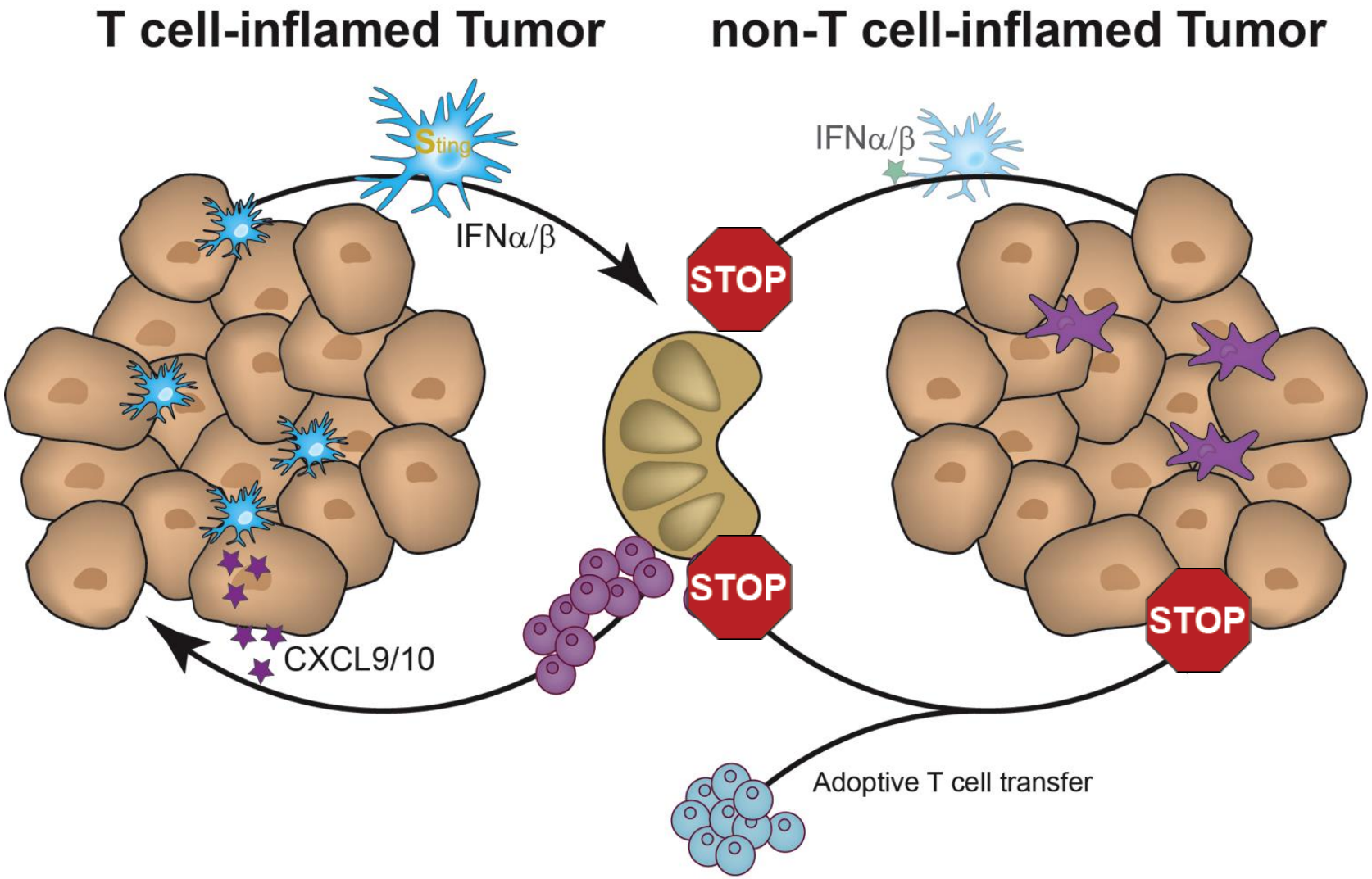
Spranger and Luke et al., PNAS 2016
Thorsson et al. Immunity 2018


Primary Tumor
Innate evasion
T cell exclusion
t
Evasion by excluding T cells
Mixed phenotype
?
Adaptive evasion
Adaptive immune resistance
t
Evasion in the presence of T cells
NO IMMUNE EDITING
IMMUNE EDITING
Immunogenic tumor cell
Nonimmunogenic tumor cell
Immune-excluding tumor cell
T cell
PD-L1

Mechanisms of immune exclusion



Mechanisms of immune exclusion



1. Which tumor cell-intrinsic signaling pathway alterations are mediating a non-T cell-inflamed tumor microenvironment?

2. Which transcriptional alterations are found primarily in secondary resistance and which are mediating T cell exclusion within a treatment naïve tumor?

3. What will be more beneficial: targeting directly the alterations in signaling pathways or changing the immune infiltrate by targeting immune cells directly?

4. What are the best approaches to a) model the non-T cell-inflamed TME in mice and b) elucidate new pathways/immunological mechanisms of T cell exclusion in humans?

1. Which tumor cell-intrinsic signaling pathway alterations are mediating a non-T cell-inflamed tumor microenvironment?

Which transcriptional signature have been defined/should be defined to study the TME.

Immune signatures:
T cells (CD8 focused)
Type-I interferon
Type-II interferon
Interferon
T cell dysfunction
T cell memory/effector
NK cells
Myeloid cells
Antigen presenting cells
Batf3-DC

1. Which tumor cell-intrinsic signaling pathway alterations are mediating a non-T cell-inflamed tumor microenvironment?

Which transcriptional signature have been defined/should be defined to study the TME.

Tumor/stroma signatures:
Mesenchymal (EMT)
DNA damage
Aneuploidy
Genomic integrity
Angiogenesis
CAF
Fibrosis
Metabolomics
Mitochondrial dynamics

Oncogenic/tumor suppressor pathways:
LKB1
CTNNB1
TGFb
PTEN
p53

1. Which tumor cell-intrinsic signaling pathway alterations are mediating a non-T cell-inflamed tumor microenvironment?

Which transcriptional signature have been defined/should be defined to study the TME.

Immune tumor interactions:
TCR sequencing and matching pMHC complexes
Paired with identification of neo-antigens

Critical points for compiling the “best” signature:
Generalizable, overcome tumor heterogeneity, testable using currently available assays

Recommendation of RNA-sequencing combined with multiplex IF

2. Which transcriptional alterations are found primarily in secondary resistance and which are mediating T cell exclusion within a treatment naïve tumor?

Academic definitions of resistance:
Primary resistance
Secondary resistance
Acquired resistance

Mouse models (mostly) one tumor

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Academic definitions of resistance:	Clinical criteria:
Primary resistance	Progressive disease
Secondary resistance	Stable disease
Acquired resistance	Complete response
Mouse models (mostly) one tumor	Patients (mostly) multiple lesions

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Academic definitions of resistance:	Clinical criteria:
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Acquired resistance	Complete response

Mouse models (mostly) one tumor	Patients (mostly) multiple lesions

Problem: not all lesions are responding equally and multiple mechanisms are at play contributing to resistance.

Lesions should be categorized independently as progressing, stable or regressing.

3. What will be more beneficial: targeting directly the alterations in signaling pathways or changing the immune infiltrate by targeting immune cells directly?

Cancer cells are driving evasion vs. immune system is not properly functioning

Targeting should be cancer type specific
Chemotherapy
Targeted therapy
Irradiation
…

Targeting can be **generalizable if mechanisms** of action applies to multiple cancer types

3. What will be more beneficial: targeting directly the alterations in signaling pathways or changing the immune infiltrate by targeting immune cells directly?

Consensus:

- Debulking
- IO interventions
- Progressive disease biomarker informed personalized decision

4. What are the best approaches to a) model the non-T cell-inflamed TME in mice and b) elucidate new pathways/immunological mechanisms of T cell exclusion in humans?

Mouse models

For exploratory/ mechanistic studies:
Models that recapitulate best the human biology (GEMM, orthotopic)

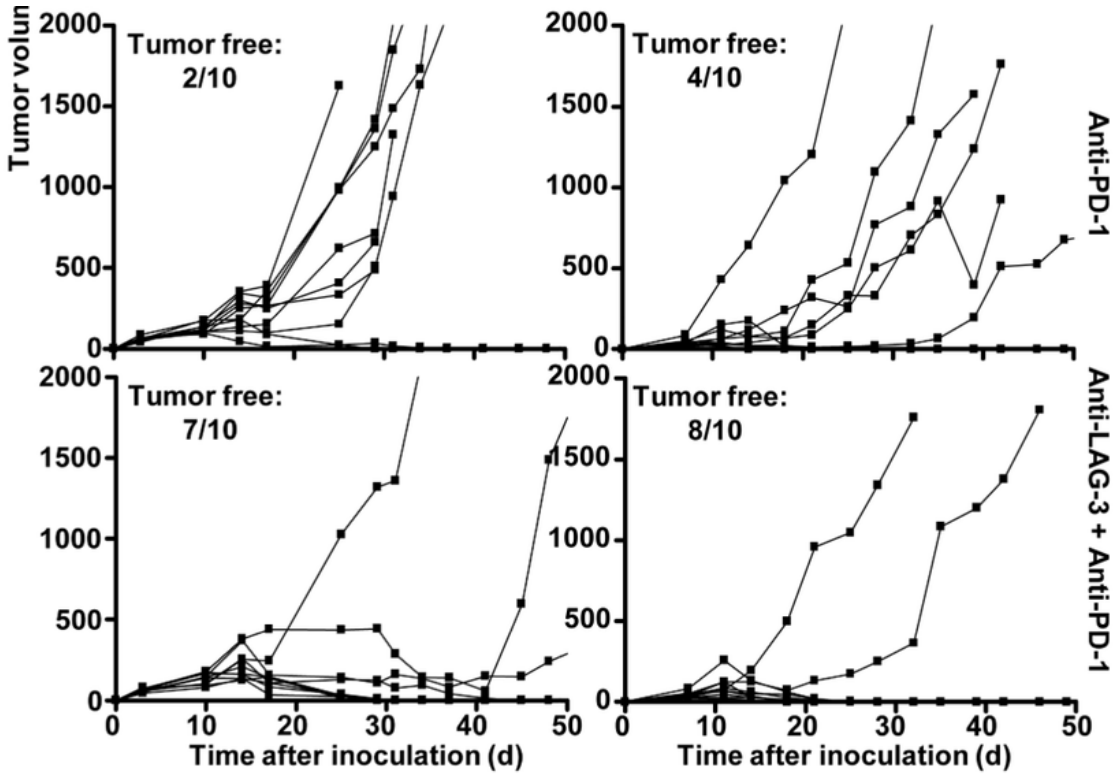
For preclinical testing:
Models that recapitulate the biology targeted (syngeneic, orthotopic)

Can we use models to understand heterogeneity in patient populations?

Mouse models

Can we use models to understand heterogeneity in patient populations?

Why are some mice not responding while littermates are?
Is there an unused opportunity?



Woo et al. (DOI 10.1158/0008-5472.CAN-11-1620)

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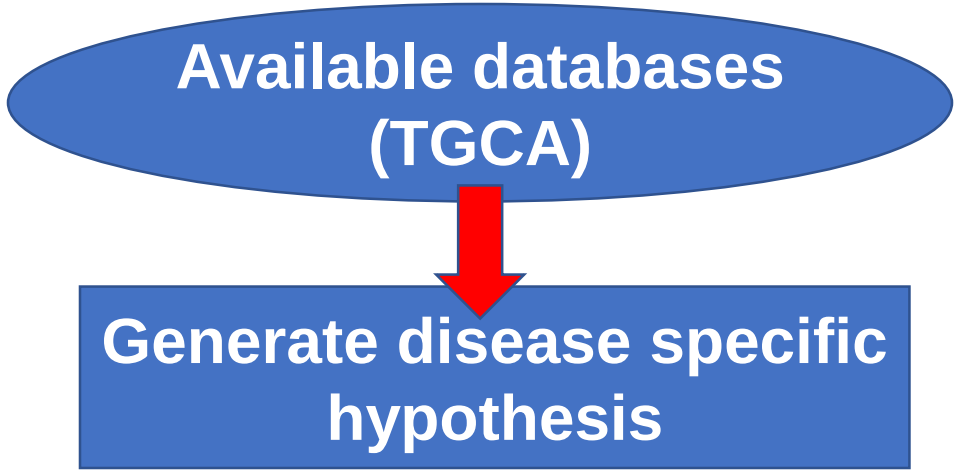
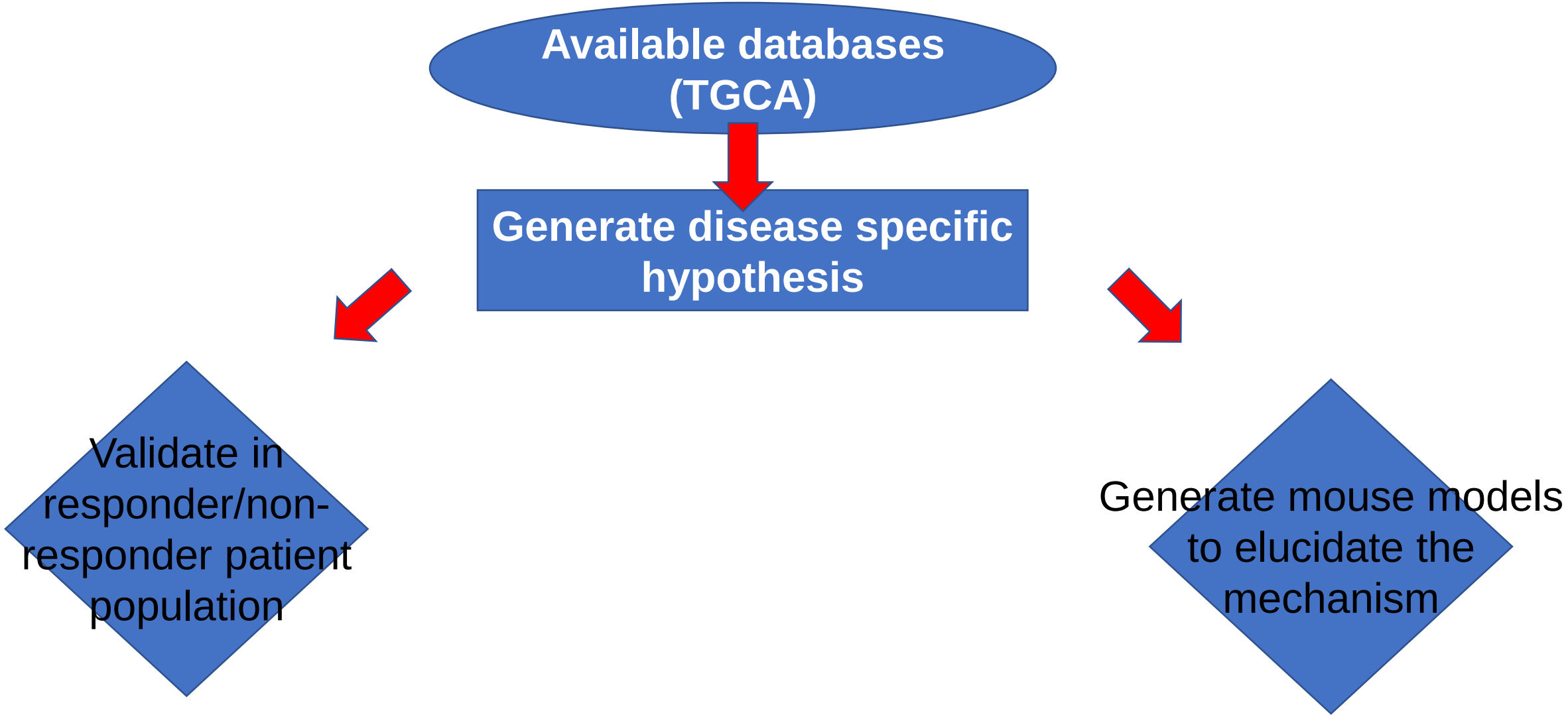
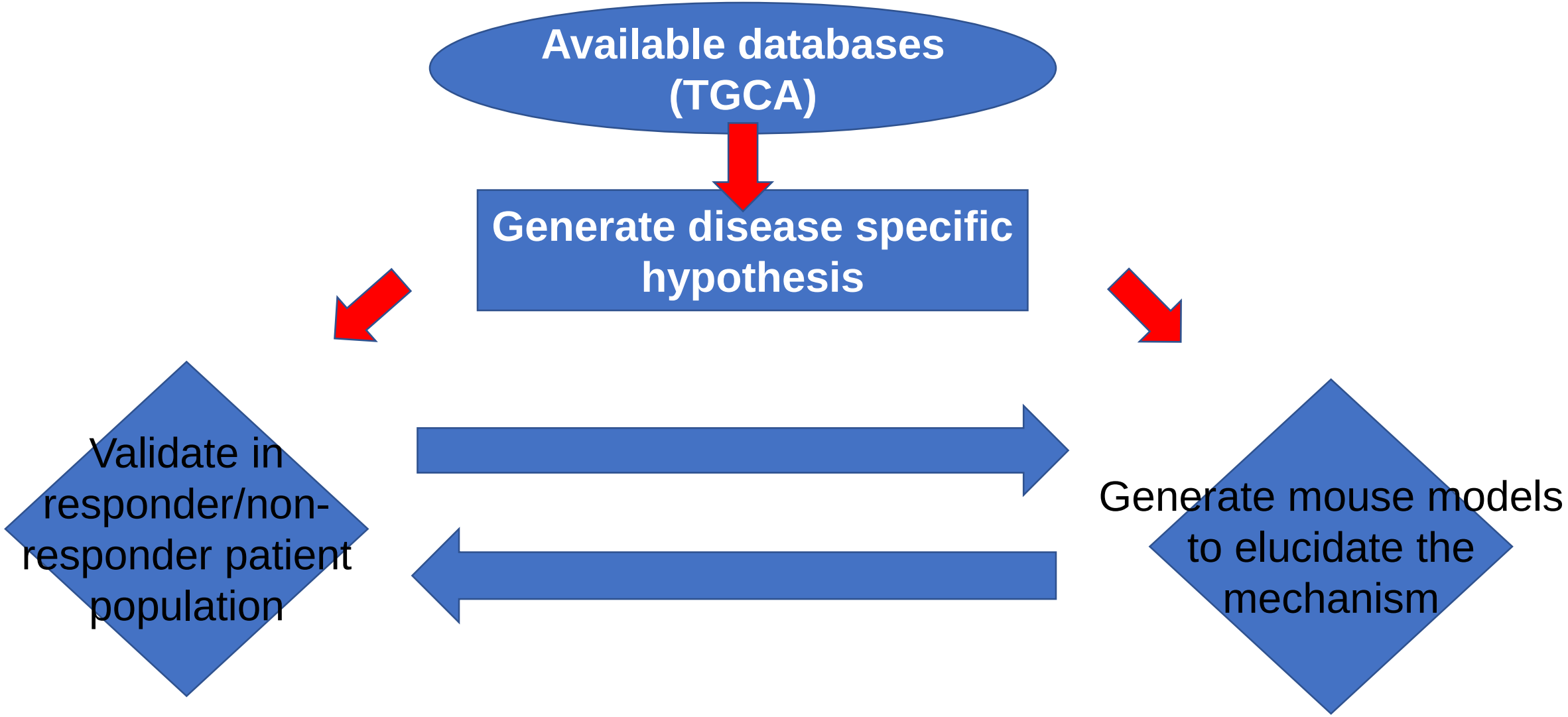
Overall approach


Available databases (TGCA)
Generate disease specific hypothesis


Available databases (TGCA)
Generate disease specific hypothesis
Validate in responder/non-responder patient population
Generate mouse models to elucidate the mechanism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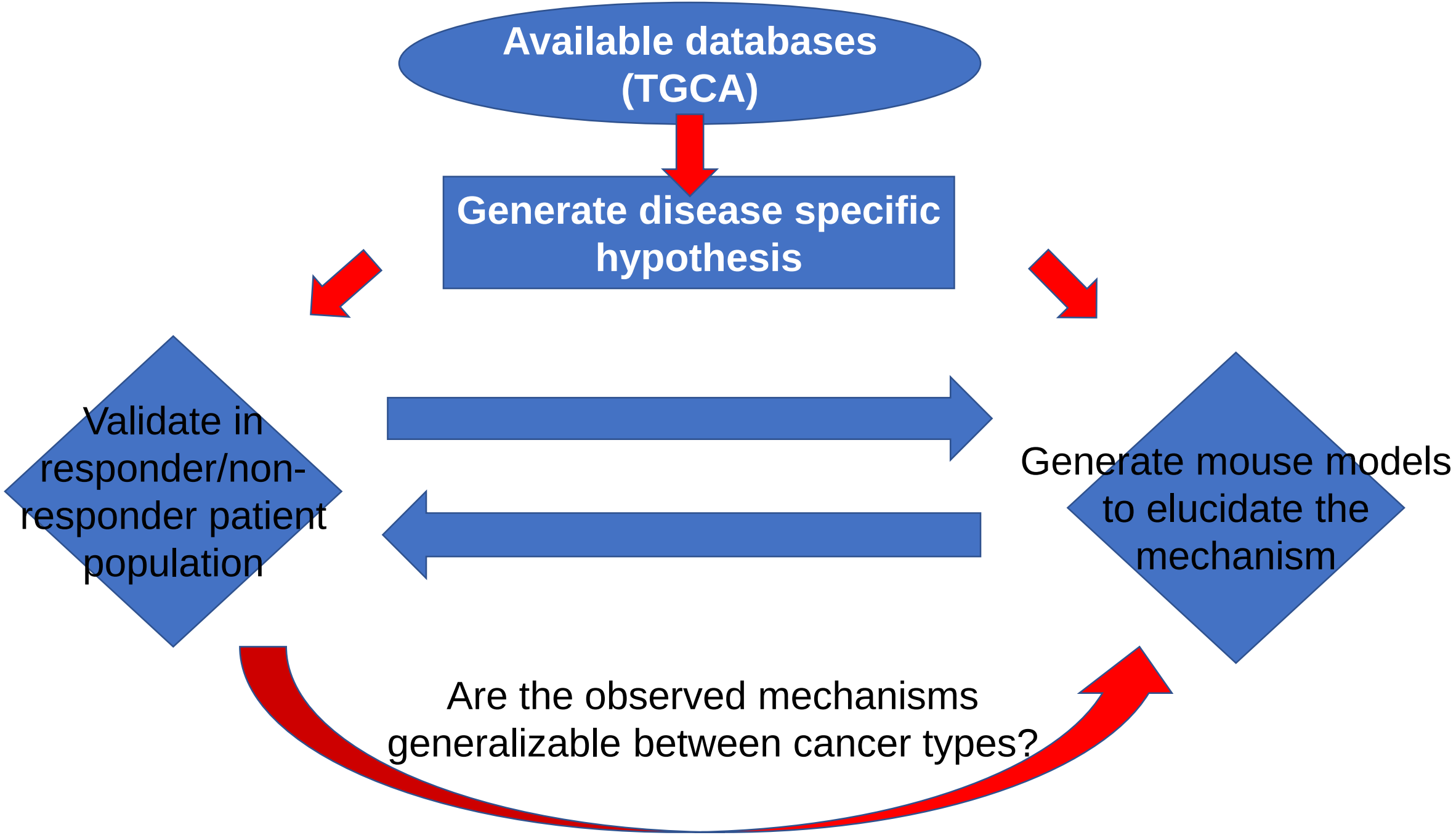
Available databases (TGCA)
Generate disease specific hypothesis
Validate in responder/non-responder patient population
Generate mouse models to elucidate the mechanism
Are the observed mechanisms generalizable between cancer types?

4. What are the best approaches to a) model the non-T cell-inflamed TME in mice and b) elucidate new pathways/immunological mechanisms of T cell exclusion in humans?

Resources:

Patient data repository to validate hypothesis

Data base for preclinical mouse models recapitulating certain TMEs