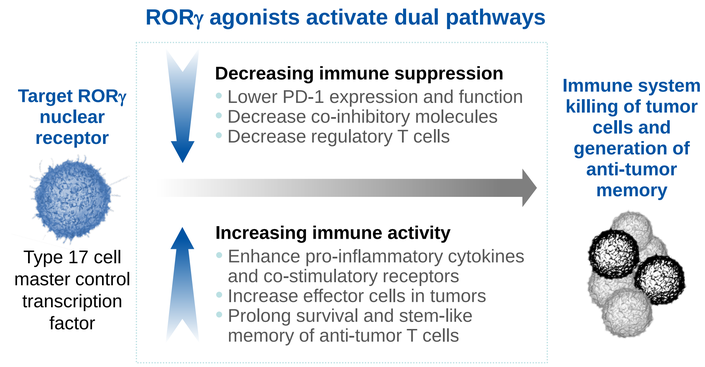
Prioritizing tumor types for treatment with a novel immunotherapy: LYC-55716 a small-molecule RORγ agonist

Xiao Hu[1], Xikui Liu[1], Hongxiu Li[1], Madhumita Bogdan[1], Yilin Gao[1], Brian Fox[2], H. Jeffrey Wilkins[3], Laura Carter[1]
[1]Lycera Corp., Ann Arbor, MI; [2]Celgene Corp., Seattle, WA; [3]Lycera Corp., Plymouth Meeting, PA.

BACKGROUND & STRATEGY

- RORγ (retinoic acid receptor–related orphan receptor γ) acts as a master control switch for the development and function of Th17 and Tc17 cells
- RORγ agonists, by enhancing Th17 and Tc17 cells, can mediate potent anti-tumor immune responses by decreasing immune suppression and increasing immune activation in preclinical studies (Figure 1) [1]
- The first-in-class, oral, small-molecule LYC-55716 is an investigational agent that selectively activates RORγ
- Phase 1 clinical testing of LYC-55716 identified a pharmacodynamically active dose and demonstrated that this agent was well tolerated in cancer patients
- In preparation for Phase 2a expansion (NCT02929862), preclinical and bioinformatics assessments were performed to prioritize tumor types to include in the Phase 1/2a clinical trial

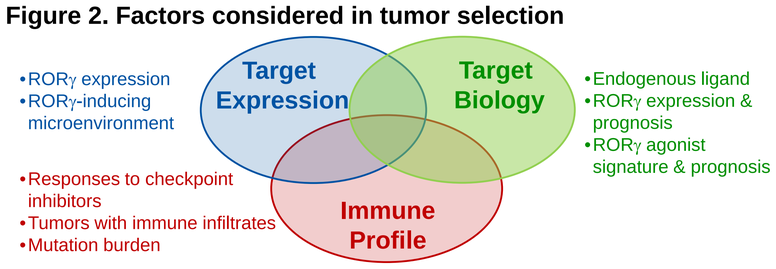
Figure 1. RORγ agonist as a novel immuno-oncology approach



Target-driven responses produce beneficial anti-tumor effects

- Bioinformatic analyses were conducted using The Cancer Genome Atlas (TCGA) dataset, to provide information across tumor types on RORγ expression and RORγ-related biology. In addition, expression of general immunologic genes associated with anti-tumor responses were also considered (Figure 2)
- For each assessment, tumor types were prioritized, then compared across categories to determine a final ranking

Figure 2. Factors considered in tumor selection



TARGET EXPRESSION

- Analysis of preclinical data indicated that the anti-tumor efficacy of an RORγ agonist was impacted by recruitment or enhancement of RORγt$^+$ cells, but not baseline RORγt levels (Figures 3 and 4)

Figure 3. Lack of correlation between baseline RORγt (RORC2) expression in tumors and RORγ agonist efficacy

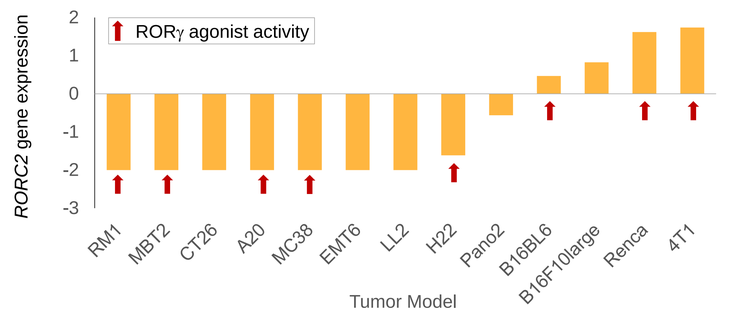
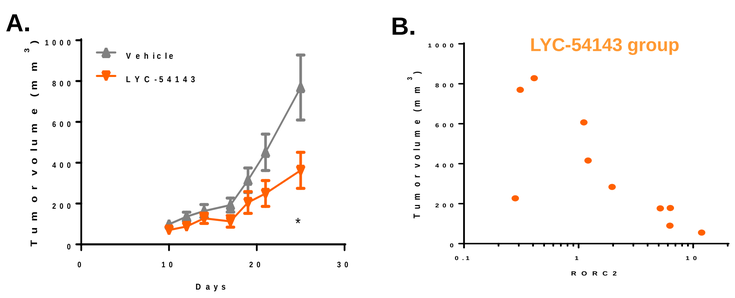
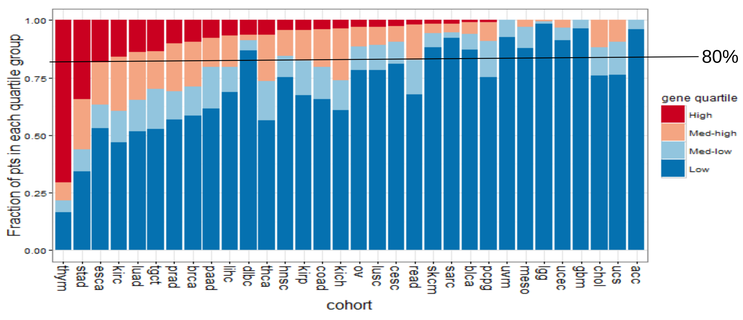


Figure 4. (A) Efficacy of RORγ agonist in MC38 tumor model; (B) Correlation with post-treatment RORγt (*RORC2*) expression



- TCGA analysis showed that different tumor types express various frequencies of RORγt (*RORC2*) (Figure 5)
- Because baseline RORγt did not affect RORγ agonist activity in preclinical models, a low threshold (>20%) of expression was used to select tumor types

Figure 5. Frequency of RORγt expression across tumor types

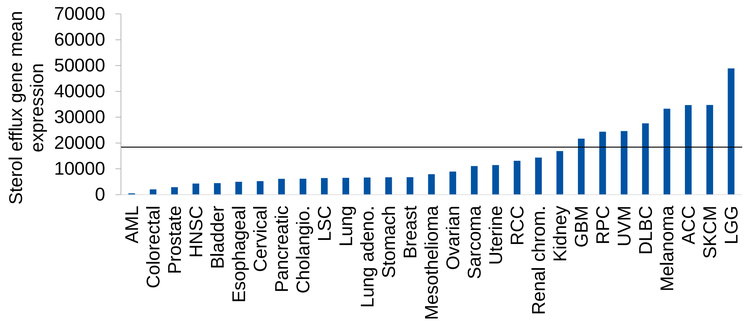


- RORγt can also be induced by cytokines such as IL6, IL1β, and IL23
  - Tumors with enriched expression of these cytokines may be more responsive to RORγ agonist therapy
- Together, these analyses identified 25 tumor types in which >20% of samples expressed RORγt or RORγ-inducing cytokines (IL6, IL1β, and IL23)

TARGET BIOLOGY

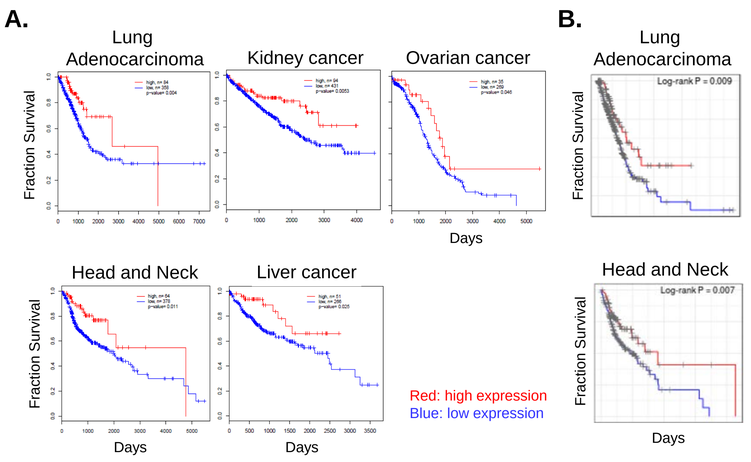
- Certain sterols can function as RORγ ligands that partially activate RORγ,[2] but sterol levels are likely low in exhausted T cells and can be influenced by cancer cells in the tumor microenvironment
- TCGA analysis of sterol efflux gene expression (a surrogate for endogenous ligand levels) revealed differential expression across tumor types (Figure 6)
  - Tumor types with low sterol efflux will likely respond better to RORγ agonist

Figure 6. Expression of sterol efflux genes across tumor types



- Analysis of TCGA data and public datasets revealed a positive correlation between RORγ/IL17 expression and patient survival in 5 tumor types (Figure 7)

Figure 7. Correlation between patient survival and expression of (A) RORγ and (B) IL17 (examples) in the TCGA datasets

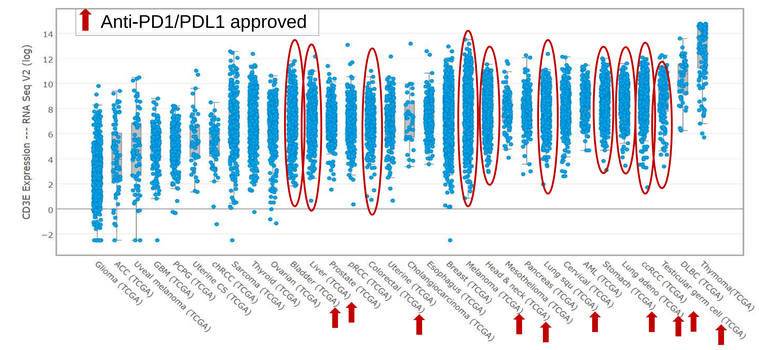


- An RORγ agonist signature was derived from transcriptional profiling of primary murine and human T cells treated with or without RORγ agonists and tested for correlation with survival in the TCGA dataset
  - This analysis identified lung, head and neck squamous cell, and esophageal/gastric cancers
- Five tumor types (renal, head and neck squamous cell, lung, ovarian and gastroesophageal cancers) were selected based on target biology (ie, low sterols and good prognosis with RORγ or signature genes)

IMMUNE PROFILE

- Analysis of TCGA RNA sequencing data indicated high expression of T cell markers such as CD3e across cancer types, including those that have been reported to respond to treatment with checkpoint inhibitors (Figure 8)

Figure 8. Tumor-infiltrating lymphocytes across tumor types



- Review of the literature indicated a high mutational burden in the checkpoint inhibitor–approved tumor types [3,4]
- Consideration of tumors with immune infiltrates, high mutational burden, and reports of prior immunotherapy responses highlighted 10 tumor types

CONCLUSION: TUMOR SELECTION

- Five tumor types were selected based on RORγ expression, RORγ biology, and immune profile criteria
- Bladder cancer (urothelial carcinoma) was also selected based on RORγ target expression and immune profile criteria
  - Literature review also indicated that IL-17 is implicated in the efficacy of Bacillus Calmette-Guérin immunotherapy [5]
- A total of 6 tumor types were prioritized for inclusion in the Phase 2a expansion (Table 1)

Table 1. Tumors Selected for Inclusion in Phase 2a Expansion

Indication
Non–small-cell lung cancer
Esophageal / gastric cancer
Head and neck squamous cell cancer
Ovarian cancer
Renal cell carcinoma
Urothelial carcinoma

REFERENCES

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ABBREVIATIONS: ACC, adenoid cystic carcinoma; AML, acute myeloid leukemia; Cholangio., cholangiocarcinoma; DLBC, diffuse large B-cell lymphoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell; LGG, low-grade glioma; LSC, lung squamous cell; Lung adeno., lung adenocarcinoma; RCC, renal clear cell; Renal chrom., renal chromophobe; RPC, renal papillary cell; SKCM, skin cutaneous melanoma; UVM, uveal melanoma.

DISCLOSURE: LYC-55716 is an investigational agent not yet approved by FDA: the safety and efficacy of LYC-55716 have not been established in patients.

CLINICAL TRIAL CONTACT: wilkins@lycera.com

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