



# Discovery of ULBP6 as a Novel Immuno-Oncology Target Using Pleiotropic Signals from 23andMe's Genetic and Health Survey Database

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# Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements regarding the future performance of 23andMe's businesses in consumer genetics and therapeutics and the growth and potential of its proprietary research platform. All statements, other than statements of historical fact, included or incorporated in this presentation, including statements regarding 23andMe's strategy, financial position, funding for continued operations, cash reserves, projected costs, plans, database growth, future collaborations, future development of therapeutic programs or products and objectives of management, are forward-looking statements. The words "believes," "anticipates," "estimates," "plans," "expects," "intends," "may," "could," "should," "potential," "likely," "projects," "continue," "will," "schedule," and "would" or, in each case, their negative or other variations or comparable terminology, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are predictions based on 23andMe's current expectations and projections about future events and various assumptions. 23andMe cannot guarantee that it will actually achieve the plans, intentions, or expectations disclosed in its forward-looking statements and you should not place undue reliance on 23andMe's forward-looking statements. The forward-looking statements contained herein are also subject generally to other risks and uncertainties that are described from time to time in the Company's filings with the Securities and Exchange Commission, including under Item 1A, "Risk Factors" in the Company's most recent Annual Report on Form 10-K, as filed with the Securities and Exchange Commission, and as revised and updated by our Quarterly Reports on Form 10-Q and Current Reports on Form 8-K. These forward-looking statements involve a number of risks, uncertainties (many of which are beyond the control of 23andMe), or other assumptions that may cause actual results or performance to be materially different from those expressed or implied by these forward-looking statements. Investors are cautioned not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made. Except as required by law, 23andMe does not undertake any obligation to update or revise any forward-looking statements whether as a result of new information, future events, or otherwise.

# Leveraging Human Genetics to Guide Drug Discovery and Development

Drug development is inefficient

- 4.5 billion average cost of drug development<sup>1</sup>
- ~90% failure rate of drugs in clinical development<sup>2-3</sup>

Genetic evidence has a positive impact on clinical success

- Drugs with human genetic evidence are
  - enriched in approved drugs
  - 2x more likely to reach approval<sup>4-6</sup>

<sup>1</sup>Schlender, M. et al. *Pharmacoeconomics*. 2021

<sup>2</sup>Thomas, D. et al. 2021

<sup>3</sup>Dowden, H. et al. *Nat Rev Drug Discov*. 2019

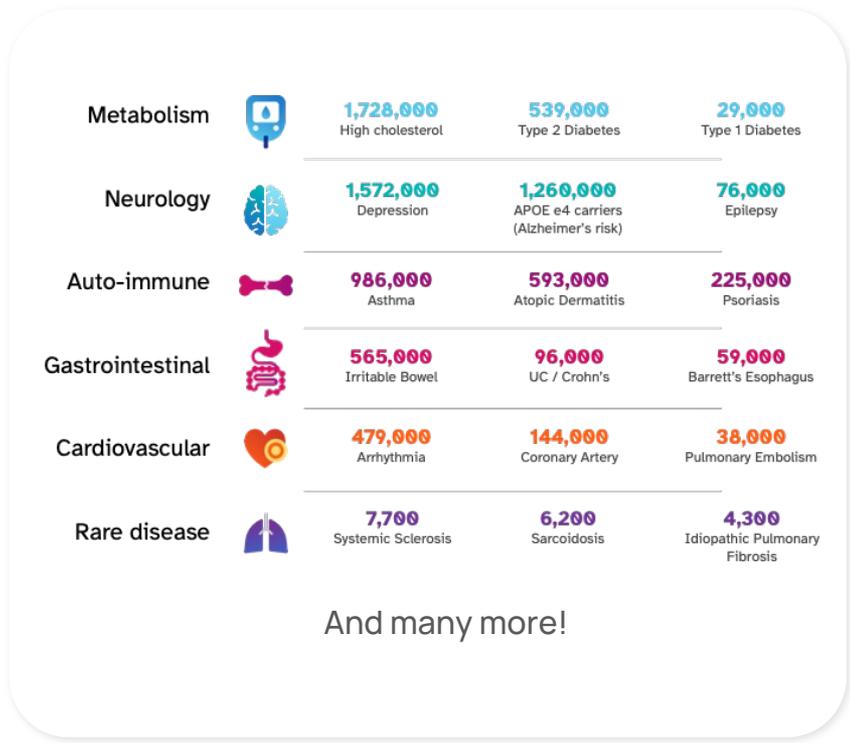
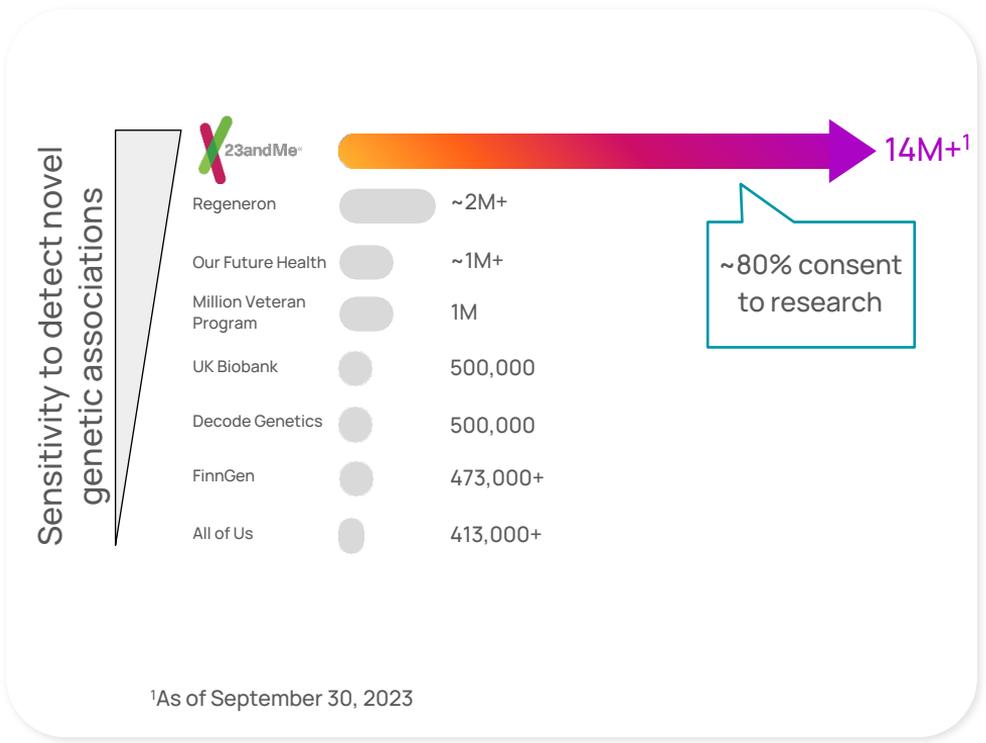
<sup>4</sup>Nelson, M.R. et al. *Nat Genet*. 2015

<sup>5</sup>King, E.A. et al. *PLoS Genet*. 2019.

<sup>6</sup>Plenge, R.M. et al. *Nat Rev Drug Discov*. 2013

# The Power of Scale

23andMe Has the Largest Re-contactable Genetic and Phenotypic Database for Target Discovery in the World



# Human Genetics and Health Information Inform Multiple Aspects of Drug Discovery and Development

23andMe Customers  
and Research  
Participants



Germline Genetic  
and Health Survey  
Data<sup>1</sup>



Genetic Analysis  
(GWAS and PheWAS)



Applications

**Target ID**



**Indication  
Expansion**



**Safety  
Risks**



**Patient  
Selection**

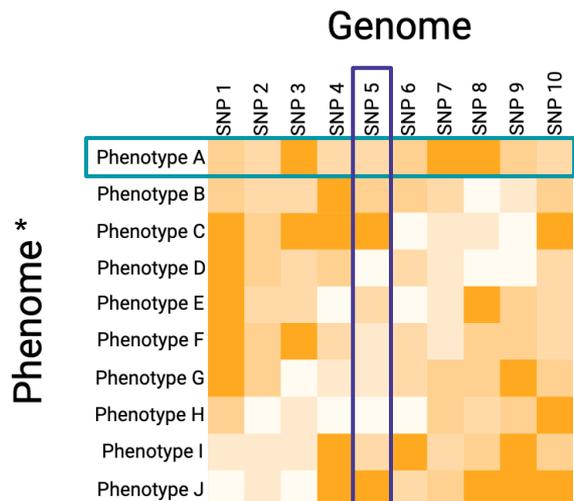


<sup>1</sup> Structured surveys

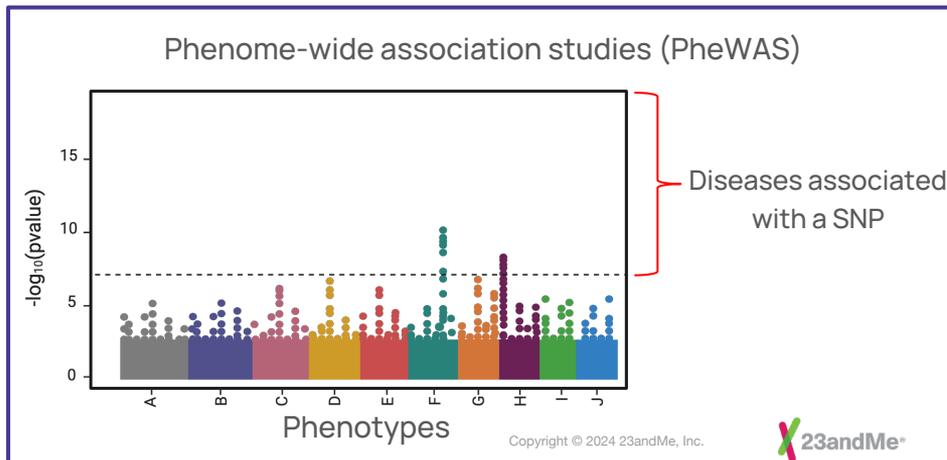
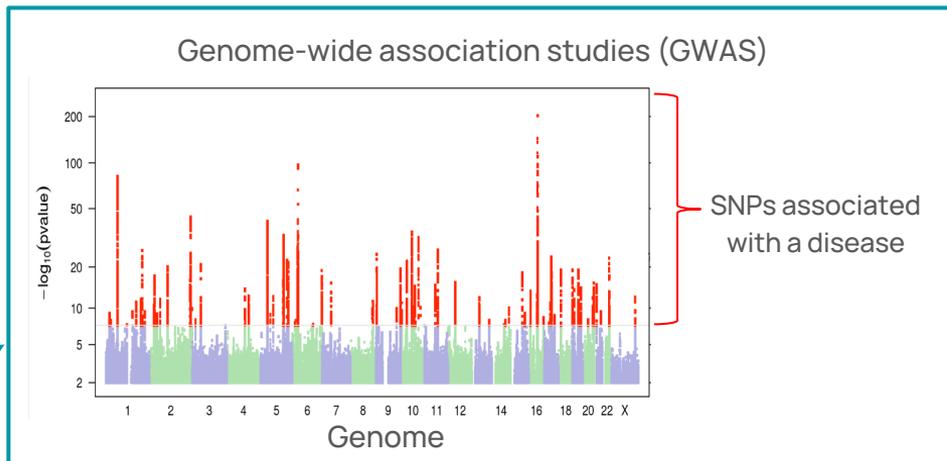
# GWAS and PheWAS are The Foundation of Genome Analysis

Single Nucleotide Polymorphism (SNP) Analysis of Germline Genome

Cases GGCCAGCTGGACGAGG  
Controls GGCCAGCTGGATGAGG

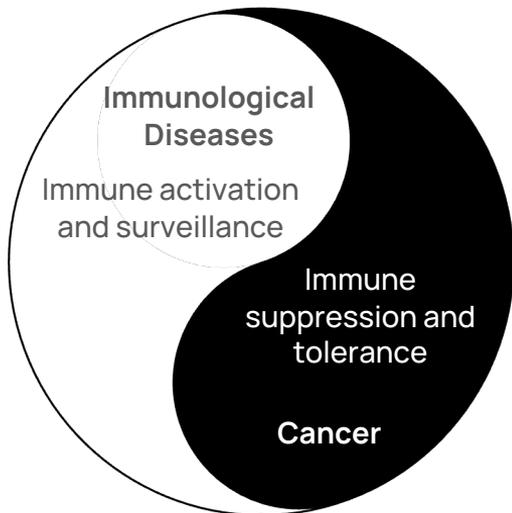


\*23andMe has >1000 medically-relevant phenotypes

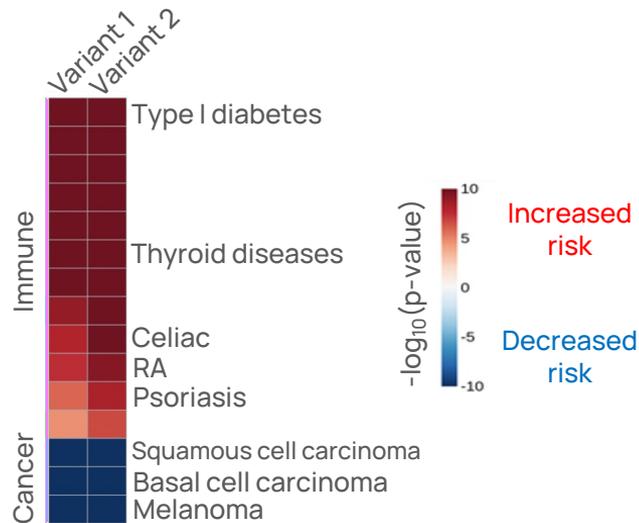


# 23andMe's Proprietary Immuno-Oncology (I/O) Signature Used to Identify Novel I/O Drug Targets

Immunological Diseases and Cancer:  
2 Sides of the Same Coin

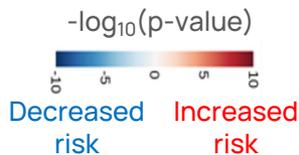
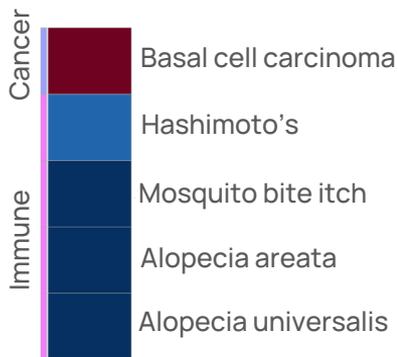


Representative *CTLA4* I/O Signature

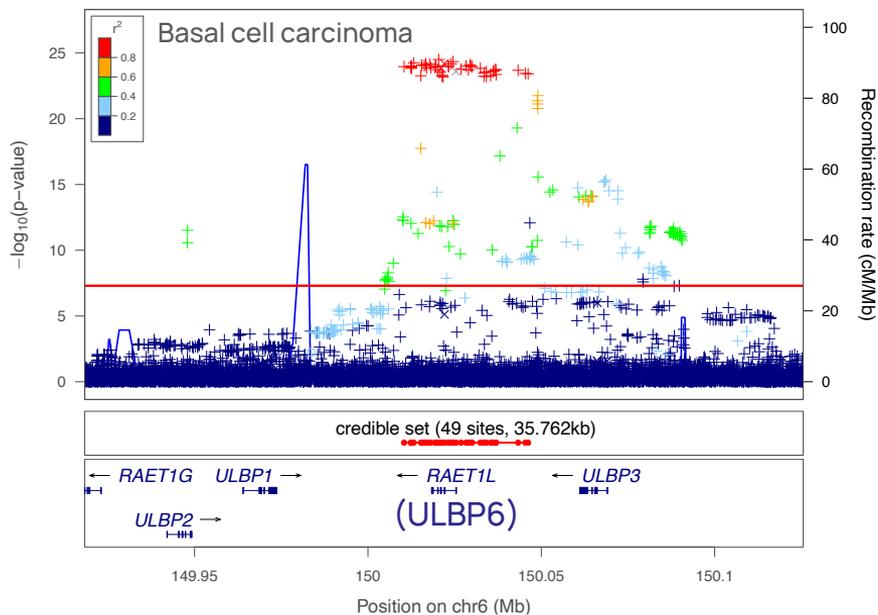


# Discovery of ULBP6 as a Cancer Therapeutic Target Using 23andMe's I/O Signature

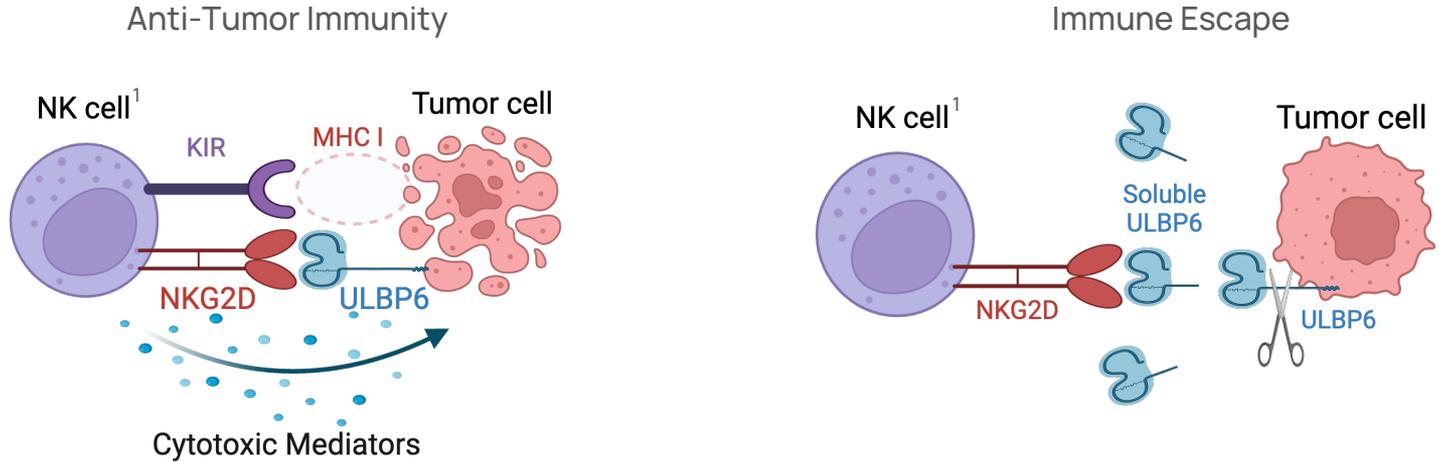
ULBP6 identified as a potentially critical immune regulator



Coding SNPs map to ULBP6



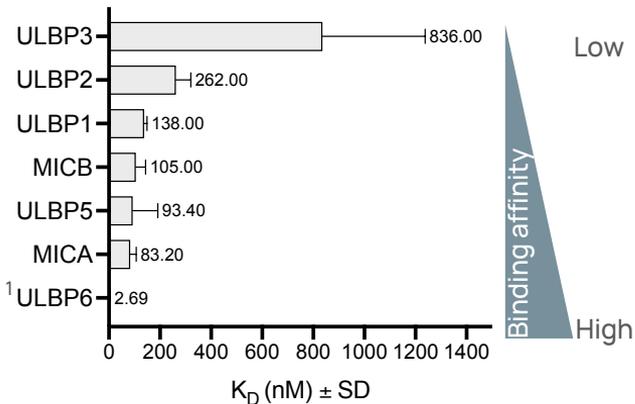
# Resistance Mechanism to T-cell Targeted Therapies Presents a Therapeutic Opportunity for NK cell Modulators



<sup>1</sup>T cell also express NKG2D

# ULBP6 May Be a Critical Regulator of Anti-Tumor Immunity as the NKG2D Ligand with the Highest Affinity for NKG2D

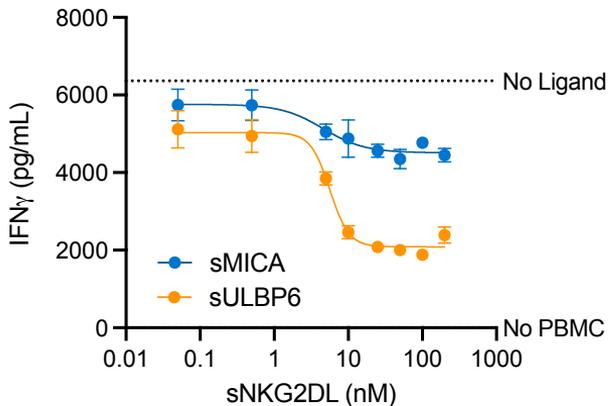
ULBP6 has the highest binding affinity for NKG2D



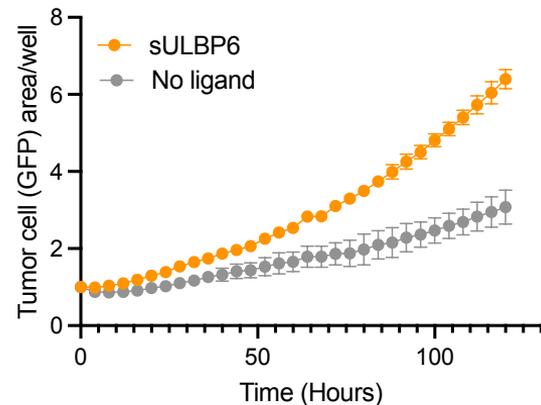
\*No binding with ULBP4

<sup>1</sup>ULBP6 isoform 1

Soluble ULBP6 is highly immunosuppressive

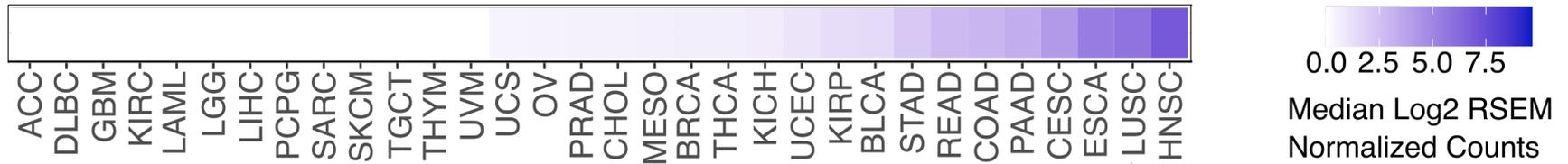


Soluble ULBP6 promotes tumor cell growth



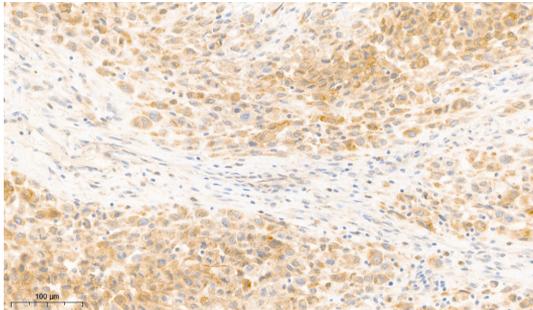
# ULBP6 is Highly Expressed in Squamous Cell Carcinomas and a Subset of Adenocarcinomas

*RAET1L* (ULBP6) mRNA expression in TCGA

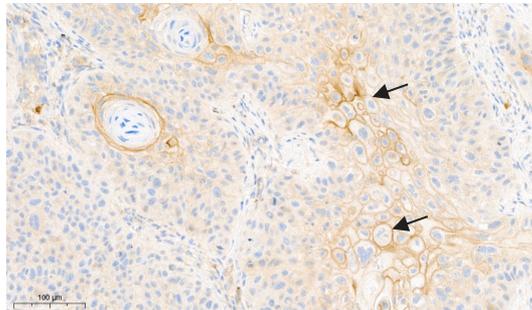


ULBP6 IHC<sup>1</sup>

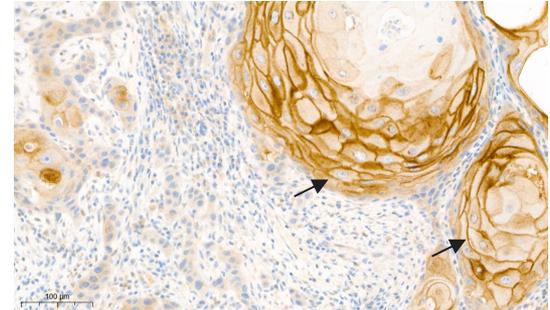
Melanoma



Lung squamous



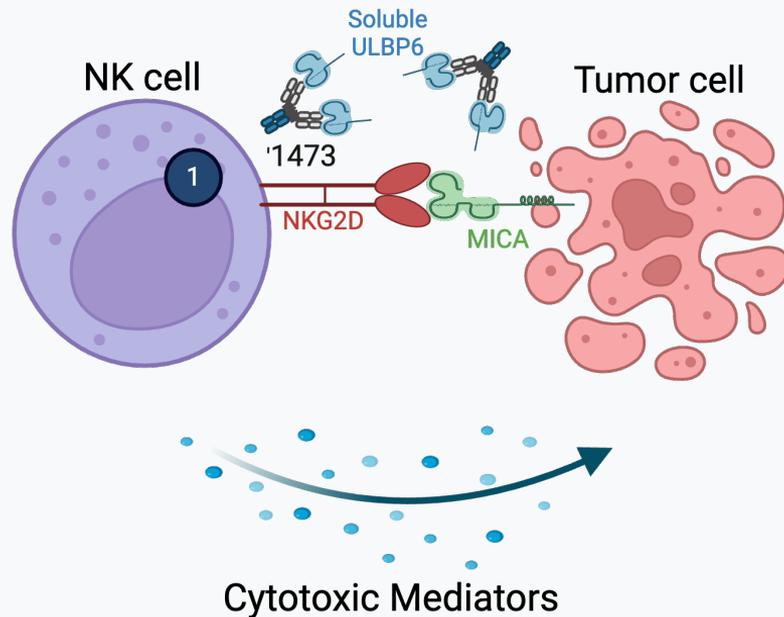
Head & neck squamous



<sup>1</sup>ULBP2 and 5 are also recognized due to high sequence homology and highly expressed in squamous cell carcinomas  
Arrows = membranous staining

# Targeting ULBP6 Is a Genetics-First Approach with Potential to Address I/O Resistance

- 23ME-01473, anti-ULBP6<sup>1</sup> humanized monoclonal antibody has dual synergistic mechanisms of action (MoA) to fully unleash NK cell activity
- **MoA 1:** Block soluble ULBP6 to reinvigorate NKG2D axis



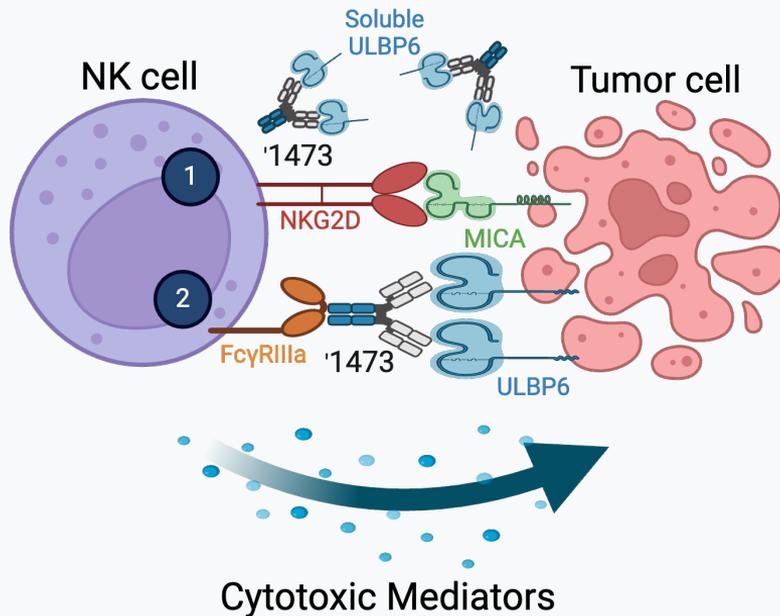
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  - MoA 1: Block soluble ULBP6 to reinvigorate NKG2D axis
  - **MoA 2**: Fc-enhanced effector function to induce ADCC
- 23ME-01473 is currently evaluated in patients with solid malignancies in a Phase 1 study

Check out Poster Abstract 2375 and <https://therapeutics.23andme.com/>



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Thank you to 23andMe Therapeutics, Research, and Consumer teams, all our customers who participate in genetic research, and patients enrolled in our Phase 1 trial!



[therapeutics.23andme.com](https://therapeutics.23andme.com)