23andMe Therapeutics

January 2024
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.
23andMe Therapeutics: Genetics Reimagining R&D

Our Value Proposition

Our credo: Every Day Matters
- Current focus: Oncology Development, Immunology Discovery
- Fast timelines and early kill decisions from discovery through clinical development to approval

Higher probability of success in the clinic
- Indication selection informed by lifetime genetic risk based on world’s largest human genotypic & phenotypic data platform
- Genetics (e.g. GWAS, PRS) and biomarkers to optimize target-indication-patient clusters

Forward-thinking expert team
- Experienced, innovative genetics researchers and clinical development team with track record for innovative approvals
- Genetics and clinical development scientists to identify higher success programs to bring into the clinic
Using Human Genetics to Create Meaningful Therapeutics for Diseases with High Unmet Need in Oncology and Immunology

NEED
Creative use of pleiotropy
Translational assays to address unmet medical needs

SPEED
Antibody and protein engineering
Pleiotropy informs clinical development and safety

Patients

POWER
Largest human genetics-based discovery platform
1000+ traits
World’s largest pleiotropy map
The Power of Our Approach
Leaders in Data

23andMe Has the Largest Recontactable Genetic Database for Target Discovery in the World

Largest, most diverse recontactable database of genotyped + phenotyped individuals

Pharma partnerships leverage the database for research and recruitment

- Target discovery
- Target validation
- Patient selection
- Clinical trial recruitment

Drugs with human genetic support are 2x - 3x more likely to succeed*

~80% consent to research

1 As of September 30, 2023.

*Publications supporting human genetic evidence for approved drug indications:
Nelson et al., 2015 (Nature Genetics); King et al., 2019 (PLoS Genetics)
### "O" Oncology phenotypes of interest (examples)

<table>
<thead>
<tr>
<th>&quot;O&quot; Oncology phenotypes</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCC</td>
<td>410,104</td>
</tr>
<tr>
<td>Bladder</td>
<td>15,663</td>
</tr>
<tr>
<td>Brain</td>
<td>4,586</td>
</tr>
<tr>
<td>Breast</td>
<td>118,632</td>
</tr>
<tr>
<td>Colorectal</td>
<td>25,398</td>
</tr>
<tr>
<td>Endometrial</td>
<td>17,912</td>
</tr>
<tr>
<td>Esophageal</td>
<td>1,134</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>8,596</td>
</tr>
<tr>
<td>Kidney</td>
<td>14,934</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,763</td>
</tr>
<tr>
<td>Liver</td>
<td>3,077</td>
</tr>
<tr>
<td>Lung</td>
<td>12,367</td>
</tr>
<tr>
<td>Melanoma</td>
<td>125,364</td>
</tr>
<tr>
<td>Myeloma</td>
<td>7,127</td>
</tr>
<tr>
<td>NH lymphoma</td>
<td>17,643</td>
</tr>
<tr>
<td>Ovarian</td>
<td>13,044</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2,910</td>
</tr>
<tr>
<td>Prostate</td>
<td>71,616</td>
</tr>
<tr>
<td>SCC</td>
<td>218,805</td>
</tr>
<tr>
<td>Stomach</td>
<td>3,508</td>
</tr>
<tr>
<td>Thyroid</td>
<td>27,269</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,133,442</strong></td>
</tr>
</tbody>
</table>

### "I" Immune phenotypes of interest (examples)

<table>
<thead>
<tr>
<th>&quot;I&quot; Immune phenotypes</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitiligo</td>
<td>60,701</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>56,233</td>
</tr>
<tr>
<td>Hashimoto's</td>
<td>186,069</td>
</tr>
<tr>
<td>IBD</td>
<td>116,788</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>716,447</td>
</tr>
<tr>
<td>Poison oak rash</td>
<td>783,604</td>
</tr>
<tr>
<td>Allergy</td>
<td>2,053,011</td>
</tr>
<tr>
<td>Food allergy</td>
<td>213,185</td>
</tr>
<tr>
<td>Asthma</td>
<td>1,128,292</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>270,499</td>
</tr>
<tr>
<td>Toenail Fungus</td>
<td>276,405</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>277,525</td>
</tr>
<tr>
<td>Hidradenitis suppurativa</td>
<td>31,008</td>
</tr>
<tr>
<td>Lupus</td>
<td>58,414</td>
</tr>
</tbody>
</table>

### Biological processes of interest captured in "I" phenotypes, not targeted in the clinic yet

- Autoimmunity
- Immune Polarization
- Atopy
- Inflammation
- Chronic Infection
- Tissue Repair

**POWER:** Combining Our “I” and “O” Phenotypes Gives Us Broad Statistical Power to Drive Unique Immunological Insights for Oncology Development
**POWER:** 23andMe Database Contains >150 Immune Disease Phenotypes With Up To 100s of Novel Genetic Insights Per Disease for Immunology Discovery

Drugs with human genetic support are **2x-3x** more likely to succeed\(^1\)

<table>
<thead>
<tr>
<th>Disease</th>
<th>23andMe GWAS cases</th>
<th>Public GWAS cases</th>
<th>23andMe hits beyond largest public GWAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>1.1M</td>
<td>65k</td>
<td>716</td>
</tr>
<tr>
<td>COPD</td>
<td>83k</td>
<td>36k</td>
<td>171</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>716k</td>
<td>84k</td>
<td>399</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>278k</td>
<td>19k</td>
<td>319</td>
</tr>
<tr>
<td>Severe acne</td>
<td>535k</td>
<td>34k</td>
<td>735</td>
</tr>
<tr>
<td>Urticaria</td>
<td>461k</td>
<td>41k</td>
<td>386</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>716k</td>
<td>84k</td>
<td>399</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>278k</td>
<td>19k</td>
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</tr>
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</tr>
<tr>
<td>Urticaria</td>
<td>461k</td>
<td>41k</td>
<td>386</td>
</tr>
<tr>
<td>Hidradenitis</td>
<td>31k</td>
<td>1.6k</td>
<td>148</td>
</tr>
<tr>
<td>Rosacea</td>
<td>352k</td>
<td>73k</td>
<td>421</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>56k</td>
<td>3k</td>
<td>67</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>61k</td>
<td>4.7k</td>
<td>75</td>
</tr>
<tr>
<td>IBD</td>
<td>117k</td>
<td>60k</td>
<td>54</td>
</tr>
</tbody>
</table>

\(^1\) 23andMe multi-ancestry meta-analysis GWAS as of October 2023

Drugs with human genetic support are more likely to succeed\(^1\)
SNPs are tested across the genome and disease associations mapped to specific regions.

GWAS: The Initial Foundation for Genome Analysis

- **Single Nucleotide Polymorphism (SNP)**
  - GGCCAGCTGGACGAGG
  - GGCCAGCTGGA
  - T
  - GAGG
- **Cases**
- **Controls**

GWAS = Genome-Wide Association Study

- SNPs associated with disease found at different frequencies in case vs controls
- Extensive know-how required to get from association to therapeutic target

SNPs are tested across the genome and disease associations mapped to specific regions.
PheWAS: Breadth of Phenotyping Elucidates Critical Disease Drivers

23andMe runs GWAS in >1,000 phenotypes

PheWAS (Phenome-Wide Association Study) captures pleiotropic effects of genetic variants and points to possible unwanted toxicities or potential indication expansions

- We observe a clear genetic signal linking TSLP to asthma
- We do not observe signals in phenotypes that would point to safety issues
- Amgen clinical trials of anti-TSLP mAb as eczema target failed. We do not observe a statistically significant genetic signal linking TSLP to eczema
- We observe a strong genetic signal linking TSLP to eosinophilic esophagitis → potential indication expansion in a rare disease
Phase 3 trial failure → Withdrawal of triple-negative breast cancer indication

N~900
HR~0.84

Germline genetic score (PRS) for hypothyroidism risk separates survival probability

N~150
HR~0.62
**POWER: Combining Extensive Pleiotropy in the 23andMe Database and Computational Biology for Target Discovery**

### Genetic insights
GWAS signals / pleiotropy (one variant affecting multiple traits)

### Computational Biology
QTL-based and custom ML models for gene mapping and target hypothesis prioritization
- Interpretation of GWAS signals making extensive use of pleiotropy and allelic series and to increase reliability of biological conclusions
- Analysis of bulk/single cell/differential gene expression

### Biological insights
Genes, mechanisms, pathways and cell types

<table>
<thead>
<tr>
<th>Disease 1</th>
<th>Disease 2</th>
<th>Disease 3</th>
<th>Disease 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal 1</td>
<td>Signal 2</td>
<td>Signal 3</td>
<td>Signal 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signal 5</th>
<th>Signal 6</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL23R</td>
</tr>
<tr>
<td>IL2</td>
</tr>
<tr>
<td>OSMR</td>
</tr>
<tr>
<td>JAK2</td>
</tr>
<tr>
<td>TYK2</td>
</tr>
<tr>
<td>IL6R</td>
</tr>
</tbody>
</table>

**Th1/Th2**
- **Th17**
- **Recept int**
- **JAK/STAT**
- **Th1/Th2 diff**
- **Th17 diff**
Utilizing the World’s Largest Human Pleiotropy Map to Address Unmet Medical Need
NEED: Our Unique Approach to De-risk Development:
Leveraging Pleiotropy to Characterize Novel Cancer Targets

23andMe “IO Signature”

23ME-00610 Lead Asset (currently in Ph2a*)

Genomic data successfully predicted '610 AE Profile

Type 1 diabetes
thyroid diseases
celiac
RA
psoriasis
SCC
BCC
Melanoma

CTLA4 gene

increased risk
decreased risk

*Currently in Phase 2a portion of Phase 1/2a
NEED: Our FxG Efforts Leverage Pleiotropy to Identify Targets in Defined Areas of Medical Need in Asthma

23andMe genetics

**23andMe** Asthma & COPD GWAS

Eczema GWAS

Bulk and single-cell RNA-seq

In vitro functional genomics

Gene Editing

NHBE cells → ALI culture → 32 days

Arrayed Library

Disease-relevant readouts

Barrier function

Cell composition & mucin production

Validated targets with pharmacologically meaningful effects in disease relevant assays
Progression of Therapeutics at Speed
**SPEED**: Our In-House Expertise in Antibody and Protein Engineering Enables Rapid Therapeutic Generation

- Experienced Antibody and Protein Engineering group
- Deep experience in protein engineering, biochemistry, structural biology, enabling diverse approaches to antibody discovery, antibody engineering, and automation
**SPEED:** Our lead IO program progressed from discovery to the clinic in 5 years

- **23andMe “IO Signature”**
  - Type 1 diabetes
  - Thyroid diseases
  - Celiac
  - RA
  - Psoriasis
  - SCC
  - BCC
  - Melanoma

- **23ME-00610 Lead Asset** (currently in Ph2a of Phase 1/2a trial)
  - CD200 Ligand
  - DOK2 Protein
  - CD200R1 Receptor

- **Genomic data successfully predicted '610 AE Profile**

  - Program initiated: 2016
  - Lead molecule generated by 23andMe
  - First human dosed: 2021
23andMe Therapeutics: Clinical Development
Experienced Clinical Development Leadership

Jennifer Low, MD, PhD
Head of Development

Genentech
Erivedge (vismodegib)
Vitrakvi (larotrectinib)
Zelboraf (vemurafenib)
Cotellic (cobimetinib)

Maike Schmidt, PhD
Sr Group Head, Translational Sciences

Genentech
FivePrime
Avastin (bevacizumab)
Tecentriq (atezolizumab)

Dylan Glatt, PhD
Sr Clinical Pharmacologist, 23ME-00610 PTL

Gilead
Jyseleca (filgotinib)
23andMe Therapeutics IO Pipeline: First-in-Class Potential

<table>
<thead>
<tr>
<th>Target Discovery</th>
<th>Lead Optimization</th>
<th>IND Enabling</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>23ME’610 anti-CD200R1</td>
<td>Solid tumors, clinical stage, IO effectorless mAb</td>
<td></td>
<td></td>
<td>Phase 2a*</td>
</tr>
<tr>
<td>23ME’1473 anti-ULBP6</td>
<td>Solid tumors, IO effector-enhanced mAb</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**23ME’610/anti-CD200R1**
- Targets Innate and Adaptive Immunity
- Potent Ab with great PK/PD
- Phase 1 monotherapy with on-target AEs
- Ph2a data expected to be presented mid-2024

**23ME’1473/anti-ULBP6**
- Activator of tumor NK cells
- Effector-enhanced Ab with dual NK-activating MOA

Note: ‘610 is in Phase 1/2a as of January 2024.
23ME-00610*

Anti-CD200R1 Antibody for Hard-to-Treat Solid Tumors Phase 1/2a

*Wholly owned; development ongoing in multiple relapsed/refractory solid tumors (including neuroendocrine and ovarian)
‘610 Development Rationale
Addressing Critical Unmet Need in Solid Tumors

Patients + Caregivers DESPERATELY seeking survival

Potential activity in >60% of current patients not deriving efficacy from PD-(L)1 inhibitors

CD200/R1 is a dominant immune checkpoint*

Highly expressed on tumor, stromal, and endothelial cells

Restricted immune expression: myeloid > T > B

Lilly’s Ucenprubart:
Clinical POC for CD200/R1 agonism in immune disease

*PMIDs: 12968329, 23662662, 22264927, 19786546, 15557172, 22264441, 34326170, 18881533, 24382916, 18999416

*PMID: 31443741; https://investor.lilly.com/static-files/9efbedo-bd6a-4d7b-823a-2996b1c2d114

*CD200R1 (inhibitory cell surface receptor), CD209 (CD200R1 ligand), and DOK2 (involved in the CD209/CD200R1 signaling pathway).

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23ME-00610 (‘610), a Fully Humanized, Effectorless IgG1, Inhibits Immunosuppressive Signaling via High Affinity Binding to CD200R1

‘610 Primary Pharmacology*

- Subnanomolar affinity
- Kills tumor cells in vitro
- Anti-tumor activity in vivo
- Potential for monotherapy
  - activity on huPBMCs that do not respond to PD-1 antibody
- Potential for combination

‘610 Clinical Development*

- Well tolerated up to 1400 mg
- PK supports Q3W (or better)
- Promising therapeutic index, projected dose ≥ ~600 mg
- Monotherapy dev ongoing
  - Further expansion in NE and OC for safety, PK, PD and dose selection
- Indication CDPs and TPPs

* PMID: 37288324

* CD266-expressing cell types include tumor, stroma and endothelial
  IFN, interferon; IL, interleukin

* Rasco, et al., 2923, SITC Annual Meeting #619; Glatt, et al., 2923 SITC Annual Meeting #699
'610 Phase 1 Results: Dose Escalation Duration of Treatment

Stable disease rate across ALL Phase 1 patients is 52% with median duration of 18.6 weeks.

Note: Treatment Duration = end of treatment date - first dose date + 1 / 365. If a participant remained on treatment at the time of data cut-off, the data cut-off date was used.

Colored portions of the horizontal bars represent the dose level the participants received. Inter-patient dose escalation to the next cleared dose level was permitted for participants who did not experience a Grade 3 or above study-drug related AE.
'610 Preliminary Clinical Activity in Neuroendocrine Cancer

- 23ME-00610 treatment was well tolerated
- 19% reduction in target lesions at Week 24 and Week 40 assessment
- 58% size reduction in longest dimension of paratracheal lesion
- Patient continues on study drug at Cycle 13 with stable disease at time of data cutoff (May 2023)
'610 Phase 2a Data: Estimated Timeline*

<table>
<thead>
<tr>
<th>2023</th>
<th>2024</th>
<th>2025</th>
<th>2026</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
</tr>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
</tr>
</tbody>
</table>

Safety: N= ≤ ~110 pts
Efficacy: N= ≤ ~90 pts

Safety: N= ≤ ~100 pts
Efficacy: N= ≤ ~75 pts

Safety: N= ≤ ~90 pts
Efficacy: N= ≤ ~60 pts

Safety: N= ≤ ~55-60 pts
Efficacy: N= ~25-30 pts

N=15 in each cohort
Enrolling
Fully Enrolled

First Efficacy Assess = i.e., Preliminary ORR, patients continue to be scanned
Safety in Phase 2a Population
Efficacy in Phase 2a Population

**ccRCC**
First Efficacy Assess
6-mo PFS/OS
12-mo PFS/OS

**OV**
First Efficacy Assess
6-mo PFS/OS
12-mo PFS/OS

**NE**
First Efficacy Assess
6-mo PFS/OS
12-mo PFS/OS

**TMB-H/MSI-H**
First Efficacy Assess
6-mo PFS/OS
12-mo PFS/OS

**SCLC**
First Efficacy Assess
6-mo PFS/OS
12-mo PFS/OS

600 mg

OV
First Efficacy Assess
6-mo PFS/OS
12-mo PFS/OS

NE
First Efficacy Assess
6-mo PFS/OS
12-mo PFS/OS

1400 mg

**ccRCC** = clear cell renal cell carcinoma
**OV** = ovarian cancer (predominantly non-clear cell histology)
**NE** = neuroendocrine

**TMB-H/MSI-H** = tumor mutational burden / microsatellite instability high tumors

SCLC = small cell lung cancer (extensive stage)

*Genotyping, tumor (archival) CD200/R1 IHC, tumor RNAseq, and pre/on-treatment tumor immunophenotyping exploratory analyses to identify potential correlates with activity

*Part of the Phase 1/2a clinical study of '610. Strictly estimated dates for discussion purposes only. Based on calendar year. Subject to change.
PBMCs from each respective patient were incubated with 100 nM of 23ME-00610, anti-PD-1, or isotype control. Cells were stimulated with SEB. IFNγ levels were determined by enzyme-linked immunosorbent assay. Mean biologic triplicates were normalized to isotype control. * p-value<=0.05 compared to control.

*610 Differentiation: Inhibition of CD200R1 Has the Potential to Address Resistance to Anti-PD1 Therapies

Blocking the CD200R1 pathway enhanced IFNγ production from SEB-stimulated PBMCs compared to isotype control and anti-PD1 in the majority of samples tested.
'610 Differentiated Combo Potential: Anti-CD200R1 with Anti-PD-1 Potentially Enhances Immune Activation

- Preliminary data from ex-vivo combination of anti-PD-1 and anti-CD200R1 blockade increased IFN\(\gamma\) (interferon-gamma) secretion from primary human T-cells

2 ug/mL per antibody. Representative data from one of four donors tested. Statistics: Ordinary one-way ANOVA with Tukey's multiple comparisons test, **p<0.01, ****p<0.0001

*23andMe internal data
'610 Next Steps

- Complete enrollment of Phase 2a Dose Expansion Cohorts
  - Recently expanded Neuroendocrine, Ovarian cohorts
  - Initial Phase 2a data cohorts planned to be presented mid-2024
  - Clinical development planning for Fast-to-Market strategies
  - Potential clinical combinations with assets with complementary mechanisms, to support earlier line indications

- Seeking partnerships to expand Phase 2a and conduct randomized Phase 2b/3 clinical trials – multiple readouts expected in 2024
23ME-01473
Genetically validated NK Cell Activator (Anti-ULBP6)
Antibody for [Metastatic] Solid Tumors
ULBP6 inhibition could benefit patients in broad range of tumor types with neoantigen loss

Dual MOA achieves synergistic NK activation and tumor cell killing

23andMe developed major methodological improvements to targeting ULBP6

External clinical validation:
Monotherapy activity observed in NKG2D pathway activator (related mechanism) with complete and partial responses at a tolerable dose in early phase clinical trial

23andMe ’1473 targets the highest affinity NKG2D ligand with a tumor cell killing-enhanced antibody

1Dhatchinamoorthy et al., Front Immunol 2021
2HNSC, Head and Neck Squamous Cancer;
3CESC, Cervical Squamous Cell Cancer

T~/~tumor~type~|~Tumor~ULBP6~|~Soluble~ULBP6~|~Loss~of~antigen~presentation\(^1\)
---|---|---|---
HNSC\(^2\)| +++| Under CDA| ++
CESC\(^3\)| +++| Under CDA| +++
Additional~tumor~types~under~CDA| +++| Under CDA| +++

MOA1
NKG2D activation

MOA2
NKG2D activation + ADCC = **23ME-01473**
Effector enhanced Fc

MOA1
Effector enhanced Fc

MOA 2
Effector enhanced Fc

23andMe, et al., CLN-619 ASCO 2023

Targeting NK cells and NKG2D shows clinical promise
’1473 Dual MOA: Effector Enhanced Antibody Binds to Tumor Cell Surface ULBP6/2/5 to Bolster NK Cell Antitumor Activity via ADCC
23andMe Therapeutics: Target Discovery
Experienced Discovery Leadership

Bill Richards
Head of Therapeutics Discovery

Vladimir Vacic
Research Fellow, Computational Biology

Patrick Collins
Director, Functional Genomics

Antony Symons
Senior Director Immunology & Inflammation

Germaine Fuh
Senior Director Antibody & Protein Engineering

Insights from the 23andMe database

Computational Biology

Functional Genomics

Immunology / Discovery Biology

Antibody Engineering

Experienced team that delivered genetics-based targets from discovery to the clinic
Hypothesis: loci associated with related phenotypes prioritize biologies not addressed by standard of care

- **eczema**: >500 loci genetic determinants of allergy/T2 inflammation
- **urticaria**: >300 loci genetic determinants of mast cell pathology
- **neuro-inflamm**: >500 loci genetic determinants of airway hyper-reactivity
- **COPD**: >200 loci genetic determinants of obstructive airway disease
- **asthma**: >600 loci genetic determinants of allergy/T2 inflammation

**Leveraging Pleiotropy to Expand Airway Target Space**

- **epithelial biology**: screen mucociliary function in ALI culture
- **sensory neuron biology**: screen in iPSC-derived neuron models
- **neuro-inflamm**: screen in IgE dependent & independent assays
- **mast cell biology**: screen in IgE dependent & independent assays
- **T2 cytokine biology**: deprioritize or develop SM/inhaled modality

Pleiotropy + functional genomics = best targets
Strategic Sequencing Based on Polygenic Risk Scores

Sequencing individuals from the tail ends of the polygenic risk score (PRS) distribution for whom the actual disease status does not match predictions.

Legend:
- cases
- controls
- selected for sequencing

Discovery of genes harboring rare variants of large effect
<table>
<thead>
<tr>
<th>Cell type</th>
<th>Disease opportunities*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage</td>
<td><strong>Broad immune</strong>: skin, lung, GI</td>
</tr>
<tr>
<td>Mast cells</td>
<td><strong>Urticaria</strong>, allergy, RA, eczema</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td><strong>Fibrosis</strong>, lung, skin, RA, IPF</td>
</tr>
<tr>
<td>T cell</td>
<td><strong>Broad immune</strong>: skin, lung, GI</td>
</tr>
<tr>
<td>Sensory Neurons</td>
<td>Respiratory, IBD, eczema</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>RA, sarcoidosis, IBD, PAH</td>
</tr>
<tr>
<td>Airway Smooth Muscle</td>
<td>Asthma, COPD, PAH</td>
</tr>
<tr>
<td>Dendritic cell</td>
<td><strong>Broad autoimmune</strong>: T1D, Graves</td>
</tr>
<tr>
<td>Keratinocytes</td>
<td>Skin</td>
</tr>
</tbody>
</table>