Targeting the Autoimmune Origins of Type 1 Diabetes

Francisco Leon, MD PhD
CSO, Provention Bio

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**Forward-Looking Statements**

This presentation contains forward-looking statements including, but not limited to, statements relating to the potential safety, efficacy, research and development efforts, regulatory review or approval and commercial viability of PRV-101 or our other product candidates as well as our business plans. “Forward-looking statements” are statements that are not historical facts and involve a number of risks and uncertainties, which may cause actual results to be materially different from any future results expressed or implied in the forward-looking statements. These statements may be identified by the use of forward-looking expressions, including, but not limited to, “expect,” “anticipate,” “intend,” “plan,” “believe,” “estimate,” “potential,” “predict,” “project,” “should,” “would,” and similar expressions and the negatives of those terms.

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The Company cautions investors not to place undue reliance on any such forward-looking statements, which speak only as of the date of this presentation. The Company does not undertake an obligation to update or revise any forward-looking statement, whether as a result of new information, future developments or otherwise, except as may be required by applicable law.

PRV-101 is investigational and not approved for any use.

The safety and efficacy of PRV-101 has not been established.
The Autoimmune Process in T1D

- Naturally occurring genetic variants confer genetic susceptibility
- In individuals with genetic predisposition, environmental factors may initiate the autoimmune process\(^1,2\)
  - Viral infections that have been shown to trigger T1D include Coxsackie B virus, enterovirus, rotavirus, influenza, mumps, rubella, and SARS-CoV-2\(^3,6\)

There are 3 Stages of T1D Progression. Autoantibodies Mark the Onset of Disease Before Symptoms Appear


<table>
<thead>
<tr>
<th>Stages</th>
<th>Pre-Symptomatic</th>
<th>Clinical (Symptomatic Requiring Insulin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Genetic risk + triggering event</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>Dysglycemia ≥2 autoantibodies</td>
<td>Diagnosis typically occurs at clinical stage 3 when a significant portion of β-cells are already lost</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Hyperglycemia ≥2 autoantibodies</td>
<td></td>
</tr>
</tbody>
</table>

Identifying T1D patients before they are symptomatic via autoantibody testing provides an opportunity to impact the normal trajectory of disease.
Nearly All Patients with Two or More T1D AAs Progress to Clinical T1D in Their Lifetime

Data from DAISY, DIPP, BABYDIAB and BABYDIET studies were combined for analysis of 13,377 children from Colorado, Finland, and Germany. FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PG, plasma glucose.

Early Stage T1D is Detected by the Presence of T1D-Related Autoantibodies\(^1\)

Antibodies against these beta cell antigens predict the development of T1D

- T1D-related autoantibodies recognize 4 main β-cell antigens
  - Glutamic acid decarboxylase (GAD65)
  - Islet antigen-2 (IA-2; ICA512)
  - Zinc transporter 8 (ZnT8)
  - Insulin (IA)

No clear order of appearance has been conclusively predictive of disease, but rather the number of autoantibodies has been shown to be predictive of disease\(^2,3\)

What Has Been Learned in Screening Studies?

Population-level screening is feasible, but efficiencies are needed to make it cost-effective for routine practice.

Targeted screening in people at risk for T1D such as first- and second-degree relatives may prevent DKA at diagnosis, but ~80% of cases are spontaneous with no family history.

Parental stress associated with a positive result was reduced with time and education.

# T1D Screening Reduced DKA Rates Across Studies and Settings

## Rates of DKA in T1D Screening Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>DKA Rate</th>
<th>Expected DKA Rate Without Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASK¹</td>
<td>GENERAL POPULATION (Colorado, USA)</td>
<td>2/13 (15%)</td>
<td>6/13 (46%)</td>
</tr>
<tr>
<td>Fr1da²</td>
<td>GENERAL POPULATION (Bavaria, Germany)</td>
<td>2/62 (3%)</td>
<td>32%</td>
</tr>
<tr>
<td>DAISY³</td>
<td>RELATIVES/GENETIC RISK (Colorado, USA)</td>
<td>1/30 (3%)</td>
<td>44/101 (44%)*</td>
</tr>
<tr>
<td>TEDDY⁴</td>
<td>GENETIC RISK, AGE &lt;5 YEARS (USA, Sweden, Finland, Germany)</td>
<td>9/79 (11%)</td>
<td>17-36%</td>
</tr>
</tbody>
</table>

*Hospitalization rate, which was mainly driven by DKA in the control patients, was reported rather than DKA in DAISY.

## T1D Screening Availability in the US is growing

<table>
<thead>
<tr>
<th>T1D Autoantibody Testing Options</th>
<th>Blood Draw Location</th>
<th>Autoantibodies Available</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial lab</td>
<td>Local lab or healthcare provider’s office</td>
<td>Blood draw</td>
<td>Varies. Generally ranges from $100 to $150 per autoantibody test</td>
</tr>
<tr>
<td>Autoimmunity Screening for Kids (ASK)</td>
<td>Barbara Davis Center, Children’s Hospital, CO. UC Health Lab Greenwood Pediatrics, At-home kit by mail</td>
<td>Blood draw or home finger poke blood test</td>
<td>GAD IA-2 Insulin ZnT8* Free if the individual meets the eligibility criteria†</td>
</tr>
<tr>
<td>TrialNet (NIDDK)</td>
<td>TrialNet-sponsored event, health fair, or at home test</td>
<td>Blood draw or home finger poke blood test</td>
<td>GAD IA-2 Insulin ZnT8 Free if the individual meets the eligibility criteria†</td>
</tr>
<tr>
<td>Enable Biosciences At-Home Test</td>
<td>Home kit. Offered as part of T1Detect Program</td>
<td>Home finger poke blood test</td>
<td>GAD IA-2 Insulin $55 or $10 if the individual is unable to afford the full price cost</td>
</tr>
</tbody>
</table>

GAD, Glutamic acid decarboxylase; IA-2, Islet antigen-2; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; T1D, type 1 diabetes; ZnT8, zinc transporter 8.

*As of 6.16.2021, ZnT8 may not be available at all testing locations.

†An individual may qualify for free autoantibody screening from TrialNet if he/she: 1) is between the ages of 2.5 and 45 years and has a parent, brother/sister, or child with T1D, is 2.5-20 years and has an aunt/uncle, cousin, grandparent, niece/nephew, or half-brother/sister with T1D, and has not been diagnosed with T1D, 2) is between the ages of 2.5 and 45 years and has tested positive for at least one T1D-related autoantibody outside of TrialNet and has not been diagnosed with T1D.

TrialNet currently does not offer rescreening to those who tested negative for autoantibodies in the past.
Estimated ~300,000 Individuals in the US at High Risk of Progression to Clinical Stage 3 T1D

People in the US are in the pre-symptomatic stage of T1D (with ≥2 autoantibodies)¹

People with ≥2 autoantibodies and abnormal blood sugars¹

T1D R&D Pipeline by Mechanism of Action and Development Phase (10/22)

Created in collaboration with SAI MedPartners.
Sources: Citeline PharmaProjects & TrialTrove (subscription services), Company Pipelines, Clinicaltrials.gov.
All products and uses of products are investigational as it relates to T1D.

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Coxsackievirus B is a Common Virus that Can Cause Acute Infection and Serious Complications

**Coxsackievirus B (CVB)**
- Human, single-stranded RNA enterovirus (EV)
- EVs are the most common infection-causing viruses in humans
  - ~10–15M non-polio enteroviral (NPEV) cases/year, including CVB (U.S.)
- CVB is one of the EV infections most frequently reported to CDC
  - 24% of NPEV infections reported to CDC during 1979–2005 were CVB

**Disease manifestations of CVB**
- While usually mild or asymptomatic, acute infections can cause severe disease
  - Including: myocarditis, aseptic meningitis, HFMD, encephalitis, otitis media
  - Acute infections of neonates can be lethal
  - Infection often severe for the immunocompromised
- CVB infection is a key trigger for autoimmunity and is associated with major chronic diseases
  - Including: type 1 diabetes, celiac disease, cardiomyopathies

No CVB vaccines are currently available

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HFMD: Hand-foot-mouth disease

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Robust Body of Evidence Suggesting a Causal Role for CVB in T1D (1 of 2)

Epidemiological association of EVs/CVBs with T1D

- Enteroviral (EV) infections are common prior to T1D diagnosis
- Vactech Oy (Finland) found CVB1-5 infection preceding insulin T1D autoantibody positivity in 50–60% of the cases. Later confirmed in 15 countries1,2
- Full virome analysis of TEDDY birth cohort identifies CVB as the only chronic viral infection associated with T1D development3
- Maternal CVB serology associated with ~50% reduction in T1D autoimmunity in offspring (Diabetes Prediction and Prevention (DIPP) study)2

1: Oikarinen et al., 2011; 2: Laitinen et al., 2014; 3: Vehik et al., 2019
Robust Body of Evidence Suggesting a Causal Role for CVB in T1D (2 of 2)

Biological support for hypothesis that CVB infection triggers T1D

- Beta cell tropism: pancreatic beta-cells strongly express coxsackie-adenovirus receptor (CAR)\(^1\)
- CAR is genetically associated with T1D\(^2\)
- EVs/CVBs identified in endocrine pancreas of T1D patients (cadaveric, living donor)\(^3,4,5\)
- EVs/CVBs cause direct damage and bystander beta cell toxic immune mechanisms
- CVB vaccine protects from infection and T1D in SOCS–1Tg mouse model\(^6\)
- Preclinical mouse studies show a protective role of anti-CVB antibodies against CVB infection and development of diabetes\(^7\)

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1: Ifie et al., 2018; 2: Vehik et al., 2019; 3: Richardson et al., 2009; 4: Krogvold et al., 2015; 5: Oikarinen et al., 2021; 6: Stone et al., 2020; 7: Larsson et al., 2013

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Preclinical Proof-of-Concept for a prototype CVB Vaccine

Stone et al, Science Advances 2019
PRV-101 is a formalin-inactivated vaccine comprising CVB serotypes 1 through 5

- All serotypes have been associated with T1D development
- Healthy adult subjects received 3 doses at monthly intervals.
- 2 dosed cohorts and a placebo cohort with subject randomized in a 3:1 fashion to receive:
  - Placebo (n=8)
  - 100 µL of PRV-101 (n=12)
  - 500 µL of PRV-101 (n=12)
Primary Endpoint: Investigate the Safety of Two Dose Levels of PRV-101 in Healthy Adult Volunteers

- No serious adverse events
- Treatment emergent adverse events (TEAE):

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>PRV-101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least 1 TEAE*</td>
<td>100%</td>
<td>95.80%</td>
</tr>
<tr>
<td>TEAE related to study drug</td>
<td>37.5%**</td>
<td>62.50%</td>
</tr>
<tr>
<td>Vaccine reactions***</td>
<td>37.50%</td>
<td>58.30%</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>37.50%</td>
<td>41.70%</td>
</tr>
</tbody>
</table>

*Headache (58.3%), injection site pain (37.5%), and nasopharyngitis (33.3%) were most common AE for PRV-101
** n=1 in placebo reported a severe TEAE (neck pain), while no severe TEAE reported for PRV-101
***Vaccine reactions: injection site pain (33.3%), headache (20.8%), injection site discomfort (16.7%), and injection site pruritus (12.5%) were the most common TEAEs considered related to PRV-101

- No adverse events of special interest
- No adverse events leading to study drug discontinuation
- No adverse events leading to study withdrawal
Viral Neutralizing Titer (VNT) in Baseline Sero-Negative Subjects: Results

Dose-dependent generation of high titers of VNT for all serotypes

- VNT assay is a plaque bio-assay where vaccinated subjects’ serum is tested for its ability to prevent infection of human fibroblasts \textit{in vitro}
- Unit is dilution (e.g., 2,000 means a 2000x dilution is needed to lose the prevention of infection)
- Descriptive study, not powered, no p value calculated
- For comparison, \textit{1/8 is protective titer for polio}
Durable Response as Evidenced by Antibody Levels at Study End

Responders are defined as:

- Proportion of subjects who were seronegative at baseline and developed high levels protective viral neutralization antibodies titers (VNT ≥ 1/8) by the end of study (6 months after last dose)

<table>
<thead>
<tr>
<th>(%)</th>
<th>Placebo</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVB1</td>
<td>14.3</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CVB2</td>
<td>0</td>
<td>60</td>
<td>90.9</td>
</tr>
<tr>
<td>CVB3</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CVB4</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CVB5</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
As an R&D Ecosystem, We Must Continue to Work Together to Find Solutions for People Living with T1D or its Predisposition

- Genetic Risk Assessment
- Primary Prevention
- Secondary Prevention
- Early Treatment of Clinical T1D
- Regenerative Medicine

Genetic predisposition
Infection and other environmental triggers
Autoimmunity against β-cell antigens
Degradation of β-cell function
Symptoms of dysglycemia and hyperglycemia
Dependence on exogenous insulin

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