SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This presentation and the accompanying oral commentary contain forward-looking statements including statements related to UNITY’s understanding of cellular senescence and the role it plays in diseases of aging, the potential for UNITY to develop therapeutics to slow, halt, or reverse diseases of aging, including for ophthalmologic and neurologic diseases, our expectations regarding potential benefits, activity, effectiveness, and safety of UBX1325 and other drug candidates, the potential for UNITY to successfully commence and complete clinical studies of UBX1325 for DME, AMD, and other ophthalmologic diseases, the expected timing of results of our studies, the timing of the expected commencement, progression, and conclusion of our studies including those of UBX1325, and UNITY’s expectations regarding the sufficiency of its cash runway. These statements involve substantial known and unknown risks, uncertainties, and other factors that may cause our actual results, levels of activity, performance, or achievements to be materially different from the information expressed or implied by these forward-looking statements, including the risk that the COVID-19 worldwide pandemic may continue to negatively impact the development of preclinical and clinical drug candidates, including delaying or disrupting the enrollment of patients in clinical trials, risks relating to the uncertainties inherent in the drug development process, and risks relating to UNITY’s understanding of senescence biology. We may not actually achieve the plans, intentions, or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions, and expectations disclosed in the forward-looking statements we make. The forward-looking statements in this presentation and the accompanying oral commentary represent our views as of the date of this presentation and oral commentary. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this presentation. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of UNITY in general, see UNITY’s most recent Quarterly Report on Form 10-Q for the quarter ended June 30, 2021, filed with the Securities and Exchange Commission on August 10, 2021, as well as other documents that may be filed by UNITY from time to time with the Securities and Exchange Commission. This presentation concerns drug candidates that are under clinical investigation which have not yet been approved for marketing by the U.S. Food and Drug Administration. They are currently limited by Federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.
EXECUTIVE LEADERSHIP TEAM
An experienced team with a track record of success

ANIRVAN GHOSH, PHD
Chief Executive Officer

JAMIE DANANBERG, MD
Chief Medical Officer

LYNNE SULLIVAN, MS
Chief Financial Officer

MIKE SAPIEHA, PHD
Chief Scientific Advisor

SUSIE LUNDEEN
Chief Human Resources Officer

ALEX NGUYEN, JD
General Counsel

JASON DAMIANO, PHD
VP of Biology

NATHAN GUZ, PHD
VP of Operations

Biogen
Roche
Lilly
Merck Serono

Biogen
AMGEN
Roivant
Alyvant

Igenica
Novartis

UNITY
UNITY IS DEVELOPING TRANSFORMATIVE MEDICINES TO SLOW, HALT, OR REVERSE DISEASES OF AGING

Targeting cellular senescence and aging-related biology

OPHTHALMOLOGY:
DME, AMD, Diabetic Retinopathy

NEUROLOGY:
Alzheimer’s, FTD, PSP (and other Tauopathies), ALS, Cognitive Disorders
UNITY OPPORTUNITY

**MISSION**

To develop transformative therapeutics to slow, halt, or reverse diseases of aging

**FOCUS**

- **Ophthalmology**: Diabetic Retinopathy (DR) / Diabetic Macular Edema (DME), Age-Related Macular Degeneration (AMD)
- **Neurology**: Frontotemporal Dementia (FTD), Progressive Supranuclear Palsy (PSP), Alzheimer’s Disease (AD), Amyotrophic Lateral Sclerosis (ALS)

**KEY MILESTONES**

- **UBX1325 (Bcl-xL) Ph1 SAD study** shows favorable safety profile and initial evidence of efficacy in advanced DME and AMD patients
- **UBX1325 Ph1 8wk nAMD** data expected in 2H2021
- **UBX1325 Ph2a Proof-of-concept study in DME** FPI June 2021; 12wk safety and efficacy data expected in 1H2022
- **Tie2 mAb (UBX2050) and α-Klotho (UBX2089)** projected to enter IND-enabling studies in 2022
## UNITY PIPELINE

Targeting Cellular Senescence and Aging-Related Biology in Indications with Established Endpoints and Well-Defined Regulatory Pathways to Approval

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>INDICATION</th>
<th>RESEARCH</th>
<th>LEAD OPTIMIZATION</th>
<th>IND-ENABLING</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPHTHALMOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bcl-xL Inhibition</td>
<td>Diabetic Macular Edema, Diabetic Retinopathy, Age-Related Macular Degeneration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UBX1325</td>
</tr>
<tr>
<td>Tie2 Activation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tie2/VEGF bi-specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEUROLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Klotho</td>
<td>Cognitive Disorders</td>
<td></td>
<td></td>
<td></td>
<td>UBX2089</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senolytics</td>
<td>Neurodegenerative Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GROWTH AREAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Mechanisms</td>
<td>Multiple Indications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UBX1325, UBX1967, UBX2050, UBX2089
SENESCENT CELLS AFFECT THE TISSUE MICROENVIRONMENT TO DRIVE DISEASE PROGRESSION

**Senescence-Associated Secretory Phenotype**

- INFLAMMATORY FACTORS: (e.g., TNF-α, IL-1α, IL-1β, IL-6, CCL11)
- PRO-FIBROTIC FACTORS: (e.g., TGFβ1, TIMP-1, MCP-1, MMPs)
- GROWTH FACTORS: (e.g., VEGF-A, PDGF, IL-8, PAI-1)

**Cellular Stress**

- Proliferating Cells
- Initiation of Senescence

**Cell Cycle Arrest**

Targeting Senescent Cells to Restore Tissue Health

Target Senescent Cells and neutralize SASP factors to eliminate root cause of disease progression

- Cellular Stress
- Accumulation of SnCs
- SnCs, Inflammation, Tissue Dysfunction
- Clearance of SnCs with Senolytic Tx
- Regeneration and Restoration of Function

Diseased Tissue → Functional Tissue

Functional Cell → Senescent Cell (SnC) → Cytokines, chemokines & matrix remodeling factors (SASP) → Macrophage → CD4+ T lymphocyte → Fibroblast
UBX1325 - Bcl-xL inhibitor
UBX2050 - Tie2 activating mAb
UNITY IS PURSUING MULTIPLE APPROACHES TO TARGET NOVEL BIOLOGY IN EYE DISEASE

Angiogenesis well understood in retinopathies, validated with anti-VEGF therapies

UBX1325, a Bcl-xL inhibitor, shows early signs of efficacy in DME patients
UBX1325 PROVIDES AN OPPORTUNITY FOR A TRANSFORMATIVE
BEST-IN-DISEASE THERAPY

Aspirational Treatment Benefits for DME and nAMD Patients

- Rapid effect with greater efficacy and durability than SoC
- Novel MOA and favorable pharmacology
- Able to use in combination with anti-VEGF agents
- Potential for improvement of retinal/choroidal blood flow
- Able to reduce ischemic regions of the retina
- Potential for disease modification
Sema3A inducible vascular permeability in diabetes cell metabolism.

14 weeks, (citrate, 10.36 ± 0.2935; STZ, 28.81 ± 2.204; p < 0.0001, n = 7).

Mice showed pathologically elevated blood glucose levels at all analyzed time points. STZ-treated mice remained at similar levels to that observed in controls.

Figure 2D shows significant retinal levels of Vegf, 3.26 ± 0.65; p = 0.0253, n = 3). Importantly, the rise in retinal Sema3A in diabetic mice was confirmed by immunofluorescence on retinal cryosections revealed that Sema3A was strongly expressed by retinal neurons of the ganglion cell layer (GCL). Immunolocalization, laser-capture microdissection of the retinal tissue from diabetic mouse retina. Immunofluorescence on retinal cryosections confirmed SEMA3A localized to retinal ganglion cells (RGCs) within the neurons of the ganglion cell layer (GCL).

We next investigated the cellular localization of Sema3A in the diabetic retina (Figures 2J-2I). From Cerani et al., 2013.

Diabetic Macular Edema (DME) shows significant retinal swelling (C) mostly in the macular and perimacular zones was noted (D).

Diabetic Macular Edema (DME) from healthy eyes (B). Similarly, immunofluorescence on retinal sections from Diabetic Retinopathy patients suffering from DME. Horizontal lines represent medians for each group. From unpublished data.

Diabetes induces senescence in the vascular unit.

Healthy microvessel

Leaky diabetic microvessel

Senescent endothelial cells (ECs) and pericytes with upregulated Bcl-xL

Sema3A expression in transcript levels for pericyte markers platelet-derived growth factor receptor-

To breakdown of barrier function and disease progression.

THERAPEUTIC STRATEGY: VASCULAR ENDOTHELIAL SENESCENT CELLS LEAD TO BREAKDOWN OF BARRIER FUNCTION AND DISEASE PROGRESSION.

Diabetes induces macular edema
UBX1325 TARGETS A NODE UPSTREAM OF ANTI-VEGF THERAPIES

Diabetes

Hypoxia
Oxidative Stress
Inflammation

Cellular Senescence

UBX1325

Inflammatory Microenvironment

Increased Vascular Permeability

DIABETES

Hypoxia
Oxidative Stress
Inflammation

Cellular Senescence

DME

**SENESCENCE BURDEN IN AMD AND DR/DME**

**SNC BURDEN**

- **NORMAL (71F)**
- **AMD (93M)**
- **DR (64M)**

- **NORMAL (71F)**
- **AMD (93M)**
- **DR (64M)**

- **INTERMEDIATE AMD (86F)**

- **SnC burden is associated with disease activity**
- **DR/DME patients show SnC in the retinal vasculature and non-neural cells in the neuronal layers**
- **AMD patients show SnC in the choroidal vasculature and RPE layer**
- **SnC is associated with location of drusen accumulation**
UBX1325 IMPROVES RETINAL VASCULATURE IN MOUSE OIR AFTER A SINGLE INJECTION

**Retinal Bcl-xL TE**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Bcl-xL TE (% of vehicle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIR</td>
<td>vehicle</td>
<td>100 ± 5</td>
</tr>
<tr>
<td></td>
<td>10pmol</td>
<td>30 ± 2</td>
</tr>
<tr>
<td></td>
<td>100pmol</td>
<td>10 ± 1</td>
</tr>
<tr>
<td></td>
<td>normoxic</td>
<td>10 ± 1</td>
</tr>
</tbody>
</table>

**Retinal caspase activation**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Caspase activation (fold over normoxic vehicle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIR</td>
<td>vehicle</td>
<td>1 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>10pmol</td>
<td>3 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>100pmol</td>
<td>5 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>normoxic</td>
<td>1 ± 0.1</td>
</tr>
</tbody>
</table>

**Neovascularization**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>% retinal area</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS-80</td>
<td>vehicle</td>
<td>1 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>3pmol</td>
<td>3 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>10pmol</td>
<td>5 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>30pmol</td>
<td>7 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>100pmol</td>
<td>9 ± 0.5</td>
</tr>
</tbody>
</table>

**Avascular area**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>% retinal area</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS-80</td>
<td>vehicle</td>
<td>1 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>3pmol</td>
<td>3 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>10pmol</td>
<td>5 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>30pmol</td>
<td>7 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>100pmol</td>
<td>9 ± 0.5</td>
</tr>
</tbody>
</table>

**UBX1325**

- Bcl-xL TE: 100 ± 5 (vehicle), 30 ± 2 (10pmol), 10 ± 1 (100pmol), 10 ± 1 (normoxic)
- Retinal caspase activation: 1 ± 0.1 (vehicle), 3 ± 0.2 (10pmol), 5 ± 0.3 (100pmol), 1 ± 0.1 (normoxic)
- Neovascularization: 1 ± 0.1 (vehicle), 3 ± 0.2 (3pmol), 5 ± 0.3 (10pmol), 7 ± 0.4 (30pmol), 9 ± 0.5 (100pmol)
- Avascular area: 1 ± 0.1 (vehicle), 3 ± 0.2 (3pmol), 5 ± 0.3 (10pmol), 7 ± 0.4 (30pmol), 9 ± 0.5 (100pmol)
BCL-XL INHIBITORS LEAD TO IMPROVEMENT IN AVASCULAR AREAS IN CONTRAST TO ANTI-VEGF TREATMENT IN MOUSE OIR

Neovascular area (% of the retina)

Avascular area (% of the retina)

Neovascularization:
- UBX1325
- UBX1967

Avascular area:
- UBX1325
- UBX1967

UBX1325 in 03% PS-80
UBX1967 in 1%DMSO/1%PS-80/20% PEG400

Aflibercept dosed at 5 μg

UBX1325 DEMONSTRATES EFFICACY IN MOUSE MODEL OF DIABETES

**VASCULAR LEAK**

Streptozotocin-induced diabetic retinopathy model

Intravitreal dosing reduces vascular leakage and protects retinal function in diabetic mice

**PHOTORECEPTOR FUNCTION**

A-wave amplitude: week 10

*Anti-VEGF: aflibercept 5 µg (Eylea)*
THERAPEUTIC HYPOTHESIS: ELIMINATION OF VASCULAR SENESCENT CELLS BY UBX1325 SHOULD RE-ESTABLISH BARRIER FUNCTION AND REVERSE DISEASE PROGRESSION IN DME AND nAMD PATIENTS
UBX1325 Phase 1
Trial Design and Summary Data

Initial 12 Patients in SAD Study

Data presented are preliminary reads prior to fully monitoring, validating, and locking the data sets.
UBX1325 CLINICAL PROGRAM

Single Injection of UBX1325

SAFETY & TOLERABILITY

Phase 1
- SAD Study - up to 10 µg
- 24 Week Follow-up
  - Ph1 12wk SAD dose-escalation cohort data
  - Ph1 8wk nAMD cohort data

SINGLE-DOSE SAFETY & EFFICACY

Phase 2a DME Study
- First patient dosed June 2021

Phase 2a nAMD Study*
- 24 Week Follow-up
  - Oct '21
  - 4Q '21
  - 1H '22

Proposed Study *
- Long-Term Follow-up
  - 12 wk Ph2a DME efficacy data
  - 8 wk Ph2a AMD efficacy data

2020
2021
2022
2023
PHASE 1 SAD STUDY ELEMENTS

Study Population

• Patients with advanced DME or nAMD with BCVA of ≥20/80 (55 ETDRS letters) in the first 2 cohorts; 20/40 (70 ETDRS letters) once MTD is established

Endpoints

• Primary Endpoints: Safety
  – Patient reported symptoms, BCVA
  – Changes noted by SLE, direct/indirect dilated ophthalmoscopy, IOP, FP, SD-OCT
  – Safety labs, symptom- and sign-directed physical exam, vital signs, ECG

• Secondary Endpoints: systemic exposure of UBX1325 and UBX0601 (parent compound)

• Exploratory Endpoints: assessment of OCT (CST, SRF, SHRF, etc.) and OCTA, FA, BCVA, FP
PHASE 1 SAD STUDY: MAJOR ELIGIBILITY CRITERIA

### Inclusion Criteria

- Patients aged ≥18 years with DME or aged ≥50 years with nAMD
- Center-involved DME with central subfield thickness (CST) ≥ 350 μm on SD-OCT at Day 1. For nAMD, active choroidal neovascularization (CNV) associated with age-related macular degeneration as evidenced on FA and SD-OCT at Day 1, including presence of intraretinal or subretinal fluid
- BCVA in the study eye ≥20/80 in the first 2 cohorts; 20/40 thereafter

### Exclusion Criteria

- Concurrent disease in the study eye or structural damage, other than DME or nAMD, that could compromise BCVA, prevent BCVA improvement, require medical or surgical intervention during the study period, confound interpretation of the results, or interfere with assessment of toxicity or CFP in the study eye.
- HbA1C ≥12
- Concomitant therapy with anti-VEGF therapies (e.g., Avastin®, Lucentis®, or Eylea®) or previous use of these agents in the study eye within 90 days of Study
Demonstrated safety and tolerability, as well as disease-relevant biologic activity

<table>
<thead>
<tr>
<th>Safe and Well-tolerated</th>
<th>Improvements in Vision</th>
<th>Improvements in Structure</th>
</tr>
</thead>
</table>
| No dose-limiting toxicities
  • Total of two nonserious, nondrug related AE’s through 12 weeks | BCVA: Gain in ETDRS Letters from Baseline
  • Overall: 8 of 12 patients showed a gain at 8 weeks and 12 weeks
  • In higher dose cohorts (5, 10 µg): 5 of 6 patients showed a gain at 8 weeks and 12 weeks | CST: Decrease from Baseline
  • Overall: 8 of 12 patients had a decrease at 8 weeks and 6 of 10 at 12 weeks*
  • In higher dose cohorts (5, 10 µg): 5 of 6 patients showed a decrease at 8 weeks and 3 out of 5 at 12 weeks**

*Excludes two rescue patients
**Excludes one rescue patient
UBX1325 WAS WELL-TOLERATED THROUGH ALL DOSES

<table>
<thead>
<tr>
<th>Measure</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammation</td>
<td>None observed</td>
</tr>
<tr>
<td>Evidence of ocular infection</td>
<td>None observed</td>
</tr>
<tr>
<td>Persistent and clinically relevant increases in intraocular pressure</td>
<td>None observed</td>
</tr>
<tr>
<td>Clinically relevant changes in BCVA</td>
<td>2 events in 2 patients*</td>
</tr>
<tr>
<td>Retinal changes as determined by color fundus photography</td>
<td>None observed</td>
</tr>
<tr>
<td>Adverse structural changes to retina as measured by SD-OCT</td>
<td>None observed</td>
</tr>
<tr>
<td>Retinal or vitreal hemorrhage</td>
<td>None observed</td>
</tr>
<tr>
<td>Structural changes by slit-lamp exam</td>
<td>None observed</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>None observed</td>
</tr>
<tr>
<td>Other clinical or laboratory assessments</td>
<td>None observed</td>
</tr>
<tr>
<td>Patient reported symptoms</td>
<td>2 decreased VA in 2 patients*</td>
</tr>
<tr>
<td>Dose-limiting toxicity</td>
<td>None observed</td>
</tr>
</tbody>
</table>

As of August 31, 2021; Data through 12 weeks post UBX1325

Safety and Tolerability acceptable to advance to additional clinical studies with UBX1325 in ocular diseases

* Same patients, not treatment-related
IMPROVEMENT IN BCVA THROUGH 12 WEEKS IN PATIENTS WITH DME

Δ BCVA (ETDRS Letters)

Weeks

Study 1325-01

1 Rescue treatment

Aflibercept (repeat dose)

Aflibercept SBA BLA 125-387

Data from Vista

Not a head-to-head trial
IMPROVEMENT IN BCVA THROUGH 12 WEEKS IN PATIENTS WITH AMD

Sac assessment of Pt 236-0015 nondrug-related progression of polypoidal choroidal vasculopathy plus co-existing other retinovascular disease
SAC assessment of Pt 236-0015 non-drug-related progression of polypoidal choroidal vasculopathy plus co-existing other retinovascular disease
REDUCTION IN CST THROUGH 12 WEEKS IN PATIENTS RECEIVING HIGHER DOSES OF UBX1325

Δ CST (µm)

Weeks

-200 -150 -100 -50 0 50 100 150

Study 1325-01

 Rescue treatment

Dashed = nAMD

5 µg

10 µg

232-0008
232-0009
229-0012
235-0013
236-0015
231-0017

UBX1325

1 Rescue treatment

RESCUE TREATMENT
Examples of Imaging Data

Normal Optical Coherence Tomograph (OCT)
DME PATIENT 232-0009, 5 µg
BCVA IMPROVED, CST DECREASED

Baseline

Week 4

CST REDUCED

Registered Image

BCVA Change from Baseline Pt 232-0009

CST Pt 232-0009

Registered Image
DME PATIENT 232-0008, 5 µg
BCVA IMPROVED, CST DECREASED

Baseline
Hyperreflective Foci
Central Cyst

Week 4

BCVA Change from Baseline Pt 232-0008

CST Pt 232-0008

Registered Image

Registered Image

Central Cyst

Weeks

Weeks

Δ BCVA

CST (µm)
nAMD PATIENT 230-0007: 1 µg
BCVA IMPROVED, CST AND SRF REDUCED

Baseline

Week 8

Hyperreflective foci

BCVA Change from Baseline Pt 230-0007

CST Pt 230-0007
nAMD PATIENT 229-0012: 5 µg
BCVA IMPROVED, CST AND SRF REDUCED

Baseline

Week 4

BCVA Change from Baseline Pt 229-0012

CST Pt 229-0012
PH2A PROOF-OF-CONCEPT STUDY DESIGN

Patient population: Patients with DME who had at least 3 anti-VEGF IVTs in the preceding 6-month period and with residual CST ≥350µm. Last anti-VEGF should be approximately 3-6 weeks prior to enrollment. 31 patients per arm.

Duration: 24 weeks

First Patient Dosed: June 2021
PHASE 2A PROOF OF CONCEPT STUDY ENDPOINTS

- Safety
- BCVA change
- CST change
- DRSS change

Proportion of patients who require 2 or more anti-VEGF

 Determination of systemic exposure

 Improvement on capillary nonperfusion

 Proportion of patients with dry retina
UBX2050
Tie-2 Agonistic Antibody for DME and AMD
TIE2 MAB REPRESENTS AN ORTHOGONAL APPROACH TO RESTORE VASCULAR INTEGRITY

- Angiogenesis well understood in retinopathies, validated with anti-VEGF therapies

**Senescence biology**

- DR & DME
- SnCs accumulate in the retina with age and diabetic disease
- SASP → ocular inflammation; abnormal blood vessel growth
- Disease → vision loss

**Vascular biology**

**Tie2 biology**

- **Diseased Vasculature**
  - Tie2 is inactivated by Ang2
  - P13-K/Akt, MAPK/Erk
  - Junctional instability
  - Pericycle death
  - Barrier integrity lost: ocular edema/critical organ edema

Tie-2 mAb explores restoring vascular function in DME/DR independent of Bcl-xLi
VALUE PROPOSITION FOR TIE2 MAB IN EYE DISEASE

CURRENT TREATMENT

- Monthly injection for 3 mon. – 2 years
  - Many with residual fluid and reduced visual acuity

- Sub-optimal patient response
  - Often switching from one VEGF to another
  - Limited options for patients who have little or no response to anti-VEGF

- Only partial response in retina
  - No therapeutic response on ischemia or poorly perfused regions of the retina

FUTURE TREATMENT

- Efficacy beyond anti-VEGF with novel MoA
  - Potential for monotherapy or in combination with anti-VEGF/UBX1325 to target novel component of vascular biology

- Potential for greater efficacy that anti-Ang2 or anti-VA2
  - Due to direct agonism of receptor to drive signaling

- Potential for improvement of Retinal/Choroidal blood flow
  - Based on ability to reduce vaso-oblitration
Ang1 = Tie2 agonist
Ang2 = context dependent Tie2 antagonist; weak competitive agonist

TIE2 IS A KEY REGULATOR OF THE VASCULAR ENDOTHELIUM

Tie2
(Tyrosine kinase with Ig and EGF homology domains-2; aka TEK)

- Receptor tyrosine kinase expressed in endothelial cells and a subset of macrophages
- Human genetic validation: Hereditary inactivating mutations in Tie2 lead to primary congenital glaucoma
- Disease-associated dysregulation of circulating Tie2 ligands contributes to pathophysiology and patient outcomes

Ang2: Released by Weibel-Palade bodies upon endothelial cell activation
Ang1: Released homeostatically by pericytes and vascular smooth muscle cells

Endothelial cell
Vascular Smooth Cell
Pericyte

VE-PTP (Tie2 phosphatase)

Akt/Erk
Permeability
Inflammation
Apoptosis
Vessel
Integrity
Quiescence
TIE2 PATHWAY DYSREGULATION LEADS TO LOSS OF BARRIER INTEGRITY

Healthy Vasculature
- Tie2 is constitutively activated by Ang1
  
  Junctional stability
  Pericyte preservation
  Barrier integrity maintained

Diseased Vasculature
- Tie2 is inactivated by Ang2
  
  Inducers of Ang-2
  - Hyperglycemia
  - Hypoxia
  - Infection
  - Cell senescence (prelim data)

  Junctional instability
  Pericyte death
  Barrier integrity lost: ocular edema/critical organ edema

Inducers of Ang-2
- Hyperglycemia
- Hypoxia
- Infection
- Cell senescence (prelim data)
TIE2 EXPRESSION DECREASES WITH AGE IN THE HUMAN EYE

Young (20-35 yo)  Old (65-84 yo)

Tie2 expression in ocular choriocapillaris is lower in aged individuals

Kim et al., Sci Adv 2019
TIE2 CONTRIBUTES TO CHOROIDAL BLOOD FLOW IN MICE

Tie2 contributes to normal adherens junctions & choroidal blood flow in aged mice

Kim et al., Sci Adv 2019
AGONISTIC TIE2 MABS INDUCE TIE2 PATHWAY ACTIVATION IN HUVECS

Target Engagement (pTie2)

IP: anti-Tie2
WB: Tie2 and pTyrosine

Downstream Pathway Activation

WB: pAKT and AKT
WB: pERK and ERK

pTyrosine
Tie2
pAKT
AKT
pERK
ERK

Tie2 activating antibodies display potencies similar to the endogenous ligand Ang1

<table>
<thead>
<tr>
<th></th>
<th>Ang1</th>
<th>Tie2-1</th>
<th>Tie2-2</th>
<th>Tie2-3</th>
<th>Tie2-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC50 (nM)</td>
<td>0.54</td>
<td>0.91</td>
<td>0.48</td>
<td>0.45</td>
<td>1.33</td>
</tr>
</tbody>
</table>
UNITY’S TIE2 ACTIVATING MAB SIGNIFICANTLY INHIBITS CNV IN MOUSE LASER MODEL

Unpublished data, funded by UNITY, from Dr. Napoleone Ferrara (UCSD)
ADMINISTRATION OF TIE2 MAB SIGNIFICANTLY REDUCES VASCULAR OBLITERATION IN OIR MODEL

Each data point represents an average of 2 eyes from single pup. Bars represent +/- SEM; N=7-8 1-way ANOVA; Tukey’s post hoc; *p<0.05; **p<0.01; ***p<0.001;

Pilot

Effect of Tie2 Ab on Vascular Obliteration in the OIR model post P12 IP administration

Effect of Tie2 Ab on Neovascularization in the OIR model post P12 IP administration

IP Administration (10mg/kg)
NEUROLOGY

Exploring senolytic approaches to reduce CNS inflammation and reverse Tau pathology
SENESCENCE DISEASE HYPOTHESIS IN THE BRAIN

SnCs accumulate in the brain, promote inflammation and Tau accumulation, and induce neurodegeneration.

REFERENCE: Chinta et al., Cellular senescence and the aging brain, Exp Gerontol. 68:3-7 (2015)
MICROGLIAL SENESCENCE ASSOCIATED FACTORS MAY BROADLY CONTRIBUTE TO NEURODEGENERATION

Homeostatic Microglia
- Brain Immunity
- Synaptic Plasticity
- Removal of cellular debris

Disease progression

Senescent Microglia
- Synaptic Attrition
- Secrete proinflammatory SASP factors
- Activate other glia

Cellular Transformation

Dementia
- Alzheimer's, FTD
- Neurotoxic accumulation of Aβ plaques and NFTs.

ALS
- Muscle atrophy from loss of innervation.

Demyelination
- Multiple Sclerosis
- Loss of myelin slows signal transduction.

Macular Degeneration
- AMD
- Vision impairment due to photoreceptor death.
SENESCENT MICROGLIA PROVOKE NEURONAL STRESS
SASP factors may regulate TAU phosphorylation and aggregation

Homeostatic Microglia
- Brain Immunity
- Synaptic Plasticity
- Removal of cellular debris

Senescent Microglia
- Synaptic Attrition
- Secrete proinflammatory factors
- Activate other glia

Disease progression
Cellular Transformation

TAU stabilizes microtubules

TAU phosphorylation and tangle formation

Tau protein tangle
Neurofibrillary tangle

Created with Biorender.com
TAU PATHOLOGY IS A COMMON FEATURE OF NEURODEGENERATIVE DISEASE INCLUDING ALZHEIMER’S & FTD/PSP

Characteristic FTD/PSP tauopathy including (A) a tufted astrocytes in mid-frontal cortex and (B) a globose neuronal tau tangle in midbrain. CBD characteristic tau pathology showing (C) glial astrocytic plaques in the mid-frontal cortex, (D) a ballooned neuron in the anterior cingulate gyrus and (E) oligodendrocyte coiled bodies in the mid-frontal cortex. Note ballooned neurons and coiled bodies may be present in other tauopathies to a lesser extent. GGT (F) globular oligodendrocytes in white matter and (G) astrocytic tau inclusions in grey matter of the mid-frontal cortex show distinct globular morphology from PSP and CBD tau pathology. AGD associated (H) small comma-shaped 4R tau reactive grains (arrows) in the amygdala.

Irwin, Parkinsonism Relat Disord, 2016
ELIMINATION OF SnCs REDUCES TAU BURDEN IN P301S TAU MOUSE MODEL

ELIMINATION OF SnCs RESTORES COGNITION IN P301S TAU MOUSE MODEL

SENESCENCE-RELATED BIOLOGY COULD HAVE BROAD IMPACT ACROSS DISEASES WITH HIGH UNMET NEED

**CORE AREAS**

**NEUROLOGY**
- AD, FTD, PSP, ALS, Cog

**OPHTHALMOLOGY**
- DR, DME, AMD

**GROWTH AREAS**

**CARDIO/ATHERO**
- Cardiac Hypertrophy, Atherosclerosis

**PULMONARY**
- Idiopathic Pulmonary Fibrosis

**LIVER/KIDNEY**
- PSC, NASH, Recurrent kidney stones

**ONCOLOGY**
- Ocular Cancers, cold/hot tumors and I/O
FINANCIAL METRICS AND MILESTONES
FINANCIAL METRICS AND MILESTONES

FINANCIALS

• $97.5 million cash, cash equivalents and marketable securities as of June 30, 2021
• Focused capital allocation to extend cash runway through the third quarter of 2022, funding UBX1325 Phase 2a proof-of-concept study and advancing pipeline programs

MILESTONES

• 1H 2021 – Completion of initial safety and tolerability assessment of UBX1325 in a Ph1 study in patients with DME and nAMD; Initial evidence of BCVA (vision) and structure improvement
• 2H 2021 – 12- and 24-week safety, tolerability, BCVA and imaging data from Ph1 SAD cohort; 8-week safety and tolerability assessment of UBX1325 in additional cohort of patients with nAMD
• 1H 2022 – 12-week data from Phase 2a proof-of-concept study in patients with DME
UNITY IS DEVELOPING TRANSFORMATIVE MEDICINES TO SLOW, HALT, OR REVERSE DISEASES OF AGING

Targeting cellular senescence and aging-related biology

OPHTHALMOLOGY: DME, AMD, Diabetic Retinopathy

NEUROLOGY: Alzheimer’s, FTD, PSP (and other Tauopathies), ALS, Cognitive Disorders