

# THERACLONE SCIENCES



*Turning the Repertoire's Most Potent Antibodies into Superior Therapeutics*

January 2012

# THERACLONE SCIENCES

## Powerful Human Antibodies for New-Generation Therapeutics

- Proprietary I-STAR™ (In-Situ Therapeutic Antibody Rescue) mAb discovery technology
  - Applicable to multiple therapeutic areas
- Rapid identification of human-derived, broadly neutralizing therapeutic antibodies (bNAbs)
  - Rare and potent antibodies to novel epitopes
- Therapeutic focus – infectious diseases and cancer
  - Strong research capabilities
    - Landmark publications in influenza and HIV
  - Established clinical pipeline targeting high unmet need infectious diseases
- Multiple strategic partnerships
- Experienced management team and top-tier investors

## Experienced Management

### **Clifford J. Stocks**

*Chief Executive Officer  
Callistoga, ICOS*

### **Eleanor Ramos, MD**

*Chief Medical Officer  
ZymoGenetics, Bristol-Myers Squibb*

### **Kristine Swiderek, PhD**

*Vice President, Research  
ZymoGenetics, City of Hope National Cancer Center*

### **Russ Hawkinson**

*Vice President, Chief Financial Officer  
Corixa, Ernst & Young*

## Distinguished Scientific Advisory Board

### **Frank Austen, MD**

*Chair, Harvard Medical School*

### **Steven Gillis, PhD**

*Founder, Immunex; Corixa Corp*

### **Laurie Glimcher, MD**

*Harvard Medical School*

### **Robert Lamb, PhD**

*Northwestern, HHMI Investigator*

### **Robert “Chip” Schooley, MD**

*UC, San Diego*

# Top-Tier Investors



**HealthCare Ventures LLC**

**AMGEN<sup>®</sup> Ventures**



ALEXANDRIA



**VERSANT<sup>SM</sup>**  
*ventures*

CANAAN PARTNERS

**ZENYAKU KOGYO CO., LTD.**

# Strategic Collaborations in Multiple Indications

## Multi-Target Antibody Discovery Collaboration



- Discovery of antibodies to infectious disease and cancer targets
- Funding >\$600M upfront and milestones plus royalties
- Theraclone – discovery; Pfizer – clinical

### **ZENYAKU KOGYO CO., LTD.**

- Pandemic stockpiles and severe seasonal influenza
- Funding >\$40M, including upfront, research funding and milestones
- Territory: ZK – Japan; Theraclone – ROW



- Identify panels of broadly neutralizing anti-HIV mAbs
- IAVI funds Theraclone mAb discovery effort
- IAVI – mAbs for vaccine; Theraclone – mAbs for therapeutics

# THERACLONE SCIENCES

## 2011 Achievements

- TCN-032 anti-influenza antibody
  - IND filed and Phase 1 trial initiated Q3 2011
- TCN-202 anti-CMV antibody
  - Demonstrated potent viral neutralization
  - FDA Pre-IND meeting Q4 2011, IND filing H1 2012
- Completed \$11.6M Series B extension
  - ARCH, Canaan, HCV, Amgen, MPM, Alexandria, Zenyaku Kogyo
- Established research collaboration with Pfizer
- Published in Nature discovery of novel anti-HIV antibodies in collaboration with IAVI and Scripps
- Recognized as Fierce 15 by FierceBiotech

# I-STAR™

Rapid Identification of Human-derived, Broadly Neutralizing  
Therapeutic Antibodies

## Generating Superior Human Antibodies for Unmet Medical Needs

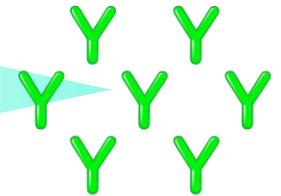
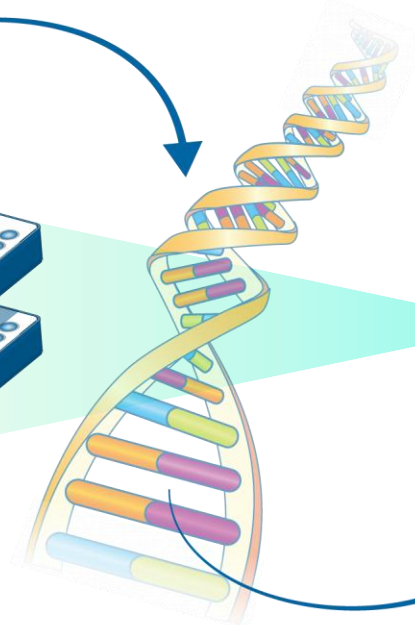
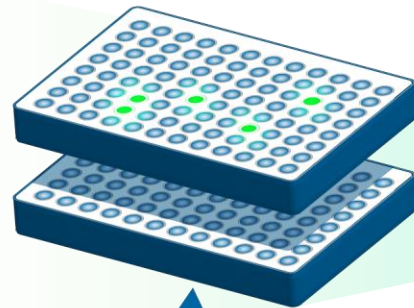
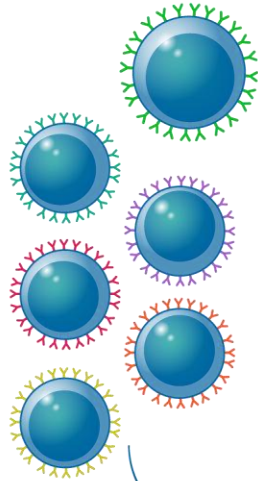
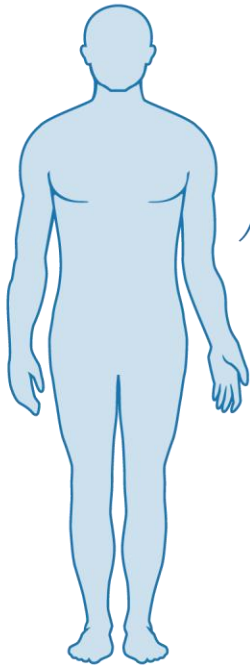
**Selected donor population**  
convalescent/vaccinated  
subjects = protective Abs

**Superior  
B-cell  
activation**

**Rapid screen for  
binding and  
function**

**Deep  
sequencing  
of all hit wells**

**Generate  
recombinant  
cell line**



**IgG+ Memory  
B-cells**  
“Archive of  
immunological history”

**>10,000  
human mAb  
clones**

**ID clones that  
neutralize/bind  
target**

**Obtain  
sequences for  
all mAbs**

**Therapeutic  
bNabs**

# Case Study – Power of I-STAR™

Discovery of Novel & Potent Broadly Neutralizing Anti-HIV Antibodies

# Protective HIV Antibodies Are Extremely Rare

## HIV is Highly Variable and Mutates Rapidly

Therapeutic Challenge – Developing an HIV Vaccine  
An effective vaccine must elicit broadly neutralizing antibodies



**Identification of new bNAbs & novel epitopes provides basis for vaccine design**

Very few HIV infected subjects make broadly neutralizing antibodies  
“Finding a needle in a haystack”



**bNAbs are rare: Only 4 discovered over past 2 decades**

# Challenge Presented to Theraclone

## Discover Novel Protective anti-HIV bNAbs

- Relevant donor pool (IAVI) ⇒ 6 HIV positive, long-term, slow progressor subjects
- Screening for function ⇒ Primary screen for viral neutralization
- >150K B cell clones screened ⇒ >17 monoclonal HIV broadly neutralizing Abs identified



### **I-STAR™ Yields Novel Broadly Neutralizing Antibodies**

- First new HIV bNAbs identified in more than 15 years
  - Broad neutralizing activity with greater potency than antibodies reported previously
  - Novel, conserved neutralizing epitopes



### **Renewed path forward for HIV vaccine development**

*Science*, 326, 2009: *Broad and Potent Neutralizing Antibodies from an African Donor Reveal a New HIV-1 Vaccine Target*, Walker et al.  
*Nature*, 477, 2011: *Broad neutralization coverage of HIV by multiple highly potent antibodies*, Walker et al.

## Platform Advantages & Differentiation

- Applicable to multiple disease indications
- Isolation of rare, protective mAbs with unique qualities from human subjects
  - Broadly neutralizing and potent antibodies
  - Identification of novel, subdominant epitopes
  - Biological relevance
- Human mAbs - Native Heavy/Light chain pairing
  - Low immunogenicity - safety
  - Efficient expression and Stability – enhanced manufacturability
- Functional screening
  - Rapid selection of relevant hits from repertoire

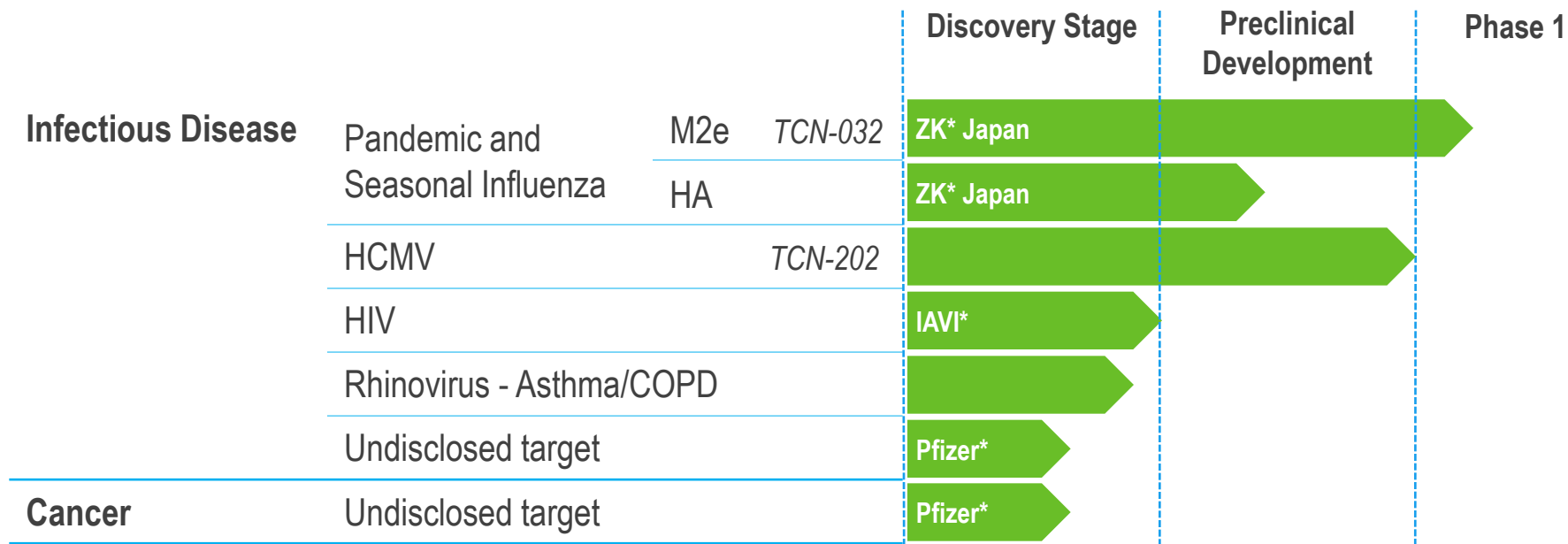
# Partnering Opportunities

I-STAR™ as Drug Discovery Engine

Clinical & Preclinical Candidates

Vaccine Discovery

## Discovery Platform Yields Broad R&D Pipeline



\*Funded Partnership

# INFLUENZA

Promising Therapeutic for Pandemic and Severe Seasonal Influenza

# Pandemic and Severe Influenza – Unmet Medical Need

## Therapeutic Challenge Represents Commercial Opportunity

- Seasonal influenza results in 200,000 hospitalizations and 30,000 deaths in the US, and 250,000 to 500,000 deaths worldwide annually
- No effective prophylactic or therapeutic option for highly pathogenic pandemic strain
- Virus' antigenic structure changes continuously limiting vaccine effectiveness
- Some strains resistant to current therapies
- Market opportunity for stockpiled therapeutic is significant

## Promising Candidate for Universal Influenza Treatment



### Human antibodies reveal a protective epitope that is highly conserved among human and nonhuman influenza A viruses

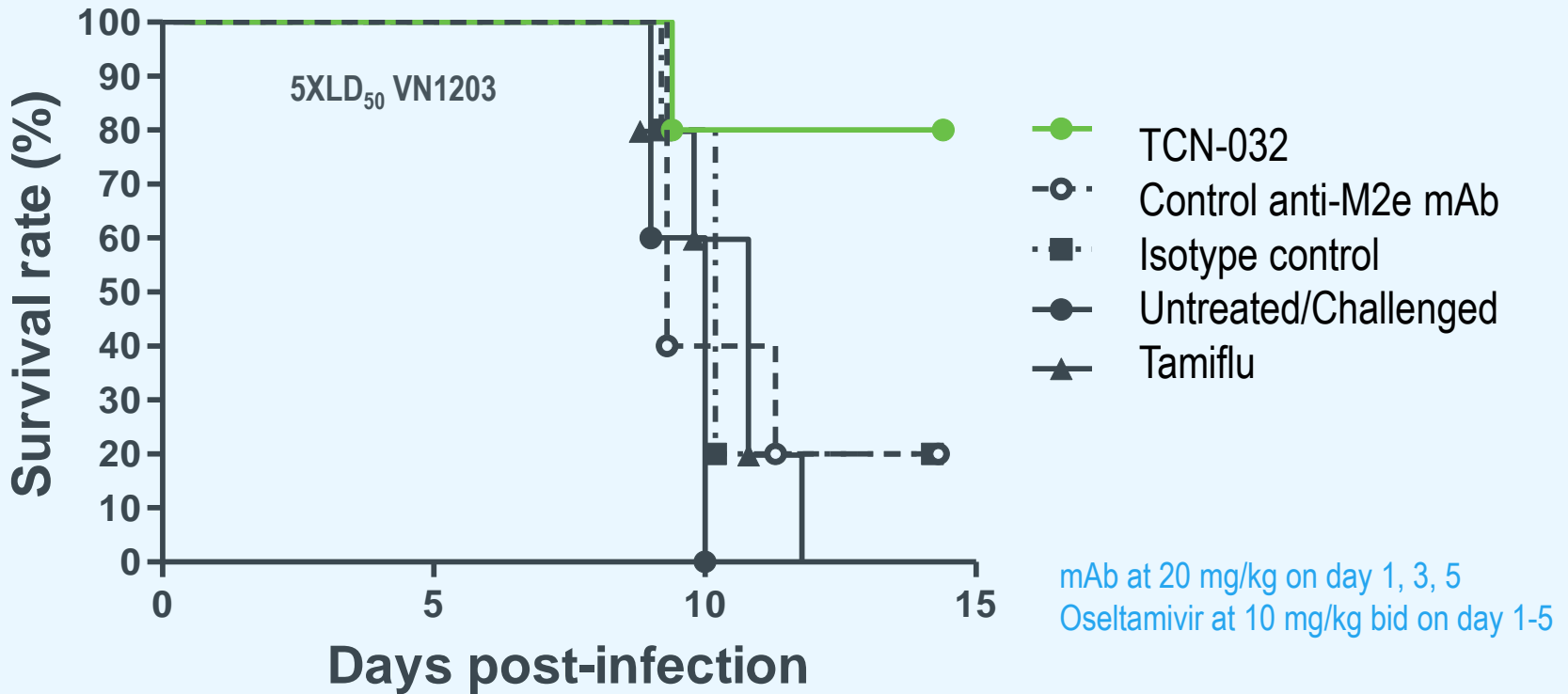
Andres G. Grandea III<sup>a,1</sup>, Ole A. Olsen<sup>a,1</sup>, Thomas C. Cox<sup>a</sup>, Mark Renshaw<sup>a</sup>, Philip W. Hammond<sup>a</sup>, Po-Ying Chan-Hui<sup>a</sup>, Jennifer L. Mitcham<sup>a</sup>, Witold Cieplak<sup>a</sup>, Shaun M. Stewart<sup>b</sup>, Michael L. Grantham<sup>b</sup>, Andrew Pekosz<sup>b</sup>, Maki Kiso<sup>c</sup>, Kyoko Shinya<sup>d</sup>, Masato Hatta<sup>e</sup>, Yoshihiro Kawaoka<sup>c,d,e,f</sup>, and Matthew Moyle<sup>a,2</sup>

<sup>a</sup>Theraclone Sciences, Seattle, WA, 98104; <sup>b</sup>The W. Harry Feinstone Department of Molecular Microbiology and Immunology, The Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, 21205; <sup>c</sup>Division of Virology, Department of Microbiology and Immunology, and International Research Center for Infectious Diseases, Institute of Medical Science, University of Tokyo, Minato-ku 108-8639, Tokyo, Japan; <sup>d</sup>Department of Microbiology and Infectious Diseases, Kobe University, Hyogo 650-0017, Japan; <sup>e</sup>Influenza Research Institute, Department of Pathological Sciences, University of Wisconsin-Madison, Madison, WI, 53792; and <sup>f</sup>Exploratory Research for Advanced Technology Infection-Induced Host Responses Project, Japan Science and Technology Agency, Saitama 332-0012, Japan

Edited\* by Francis V. Chisari, The Scripps Research Institute, La Jolla, CA, and approved June 1, 2010 (received for review October 12, 2009)

- Antibody recognizes highly conserved epitope (M2e): present in 98% of influenza A viruses
- Mechanism of Action: antibody-mediated killing of virus and infected cells
  - Nanomolar potency
- Demonstrated in vitro and in vivo efficacy in animal models of influenza

# Superior Efficacy of TCN-032 vs. Tamiflu Protects Mice in Lethal Challenge Model

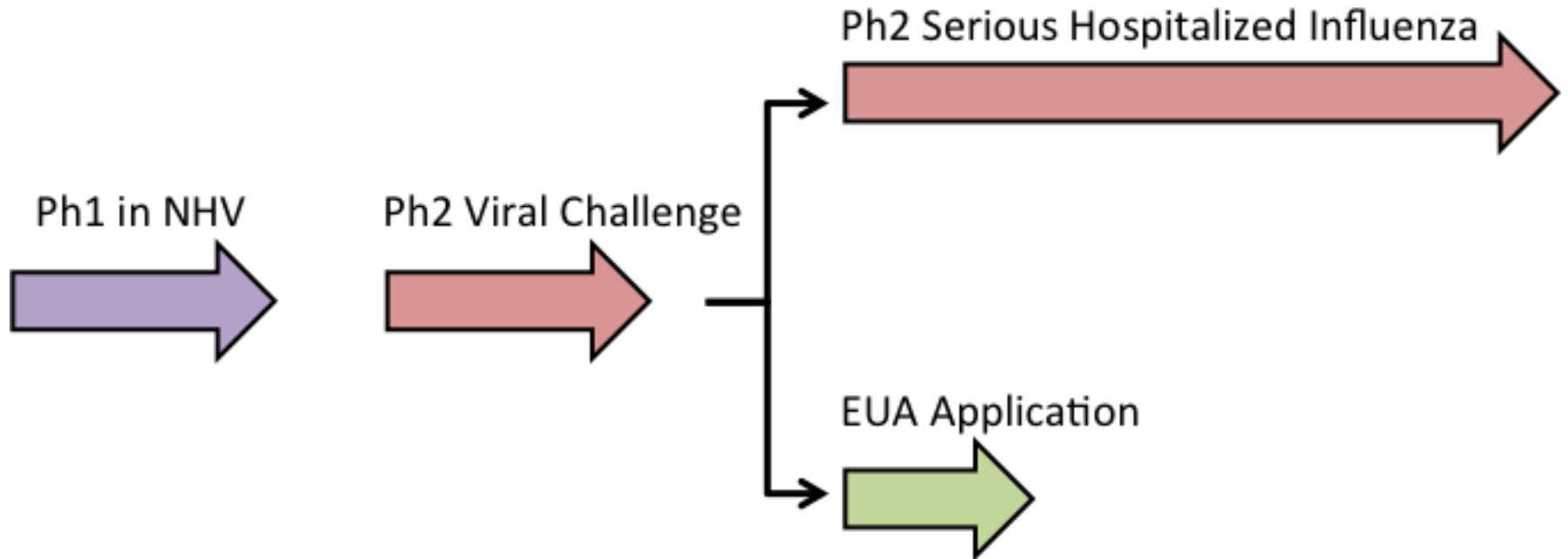


Y. Kawaoka & Hatta Masato (U of WI, Madison)



# TCN-032

## Clinical Development Strategy



### Phase 1 – NHV

- Single ascending dose (5 dose levels)
- Objectives: Safety, pharmacokinetics (PK)
- Topline data: 1H 2012

# HCMV

A Novel Antibody Addressing an Unmet Medical Need

# Therapeutic Approach

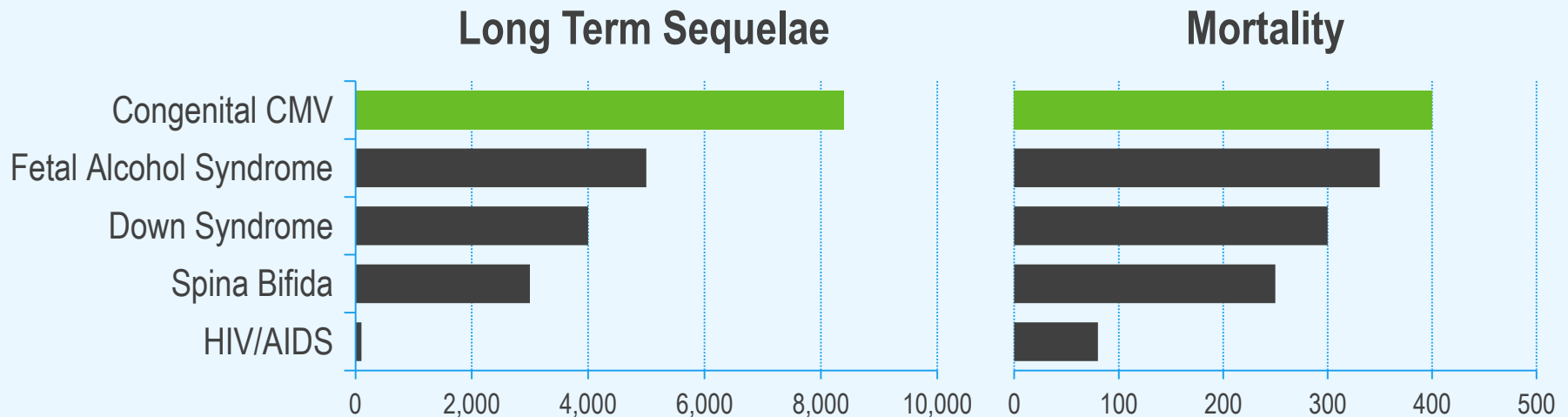
## HCMV Disease – Transplantation

- Solid organ transplant
  - Target patient population: Sero-negative recipients of organs from sero-positive donors (“D+/R-”)
- Current standard of care
  - Prophylaxis, pre-emptive or acute treatment with small molecule anti-virals or plasma-derived CMV immunoglobulin (CMV Ig)
  - Associated with significant toxicities
    - Bone marrow toxicity
    - Delayed onset of CMV disease
    - Adventitious infectious agents
  - Reduction in CMV disease with current therapy only ~ 50%
- Need for more effective and safer therapy

# Therapeutic Approach

## HCMV Disease – Congenital Infection

- Pregnancy: maternal transmission leading to congenital/neonatal infection
- Most prevalent congenital infection → causes significant morbidity and mortality
  - Acute clinical disease: liver and bone marrow toxicities
  - Permanent neurological disabilities: hearing/vision loss, mental retardation
- Current therapeutic options
  - Plasma-derived CMV Ig (adventitious infectious agents)
  - Small molecule anti-virals contra-indicated (teratogenic, genotoxic, carcinogenic)



Source: Cannon and Finn Davis; BMC Public Health 2005, 5:70  
Annual incidence in US

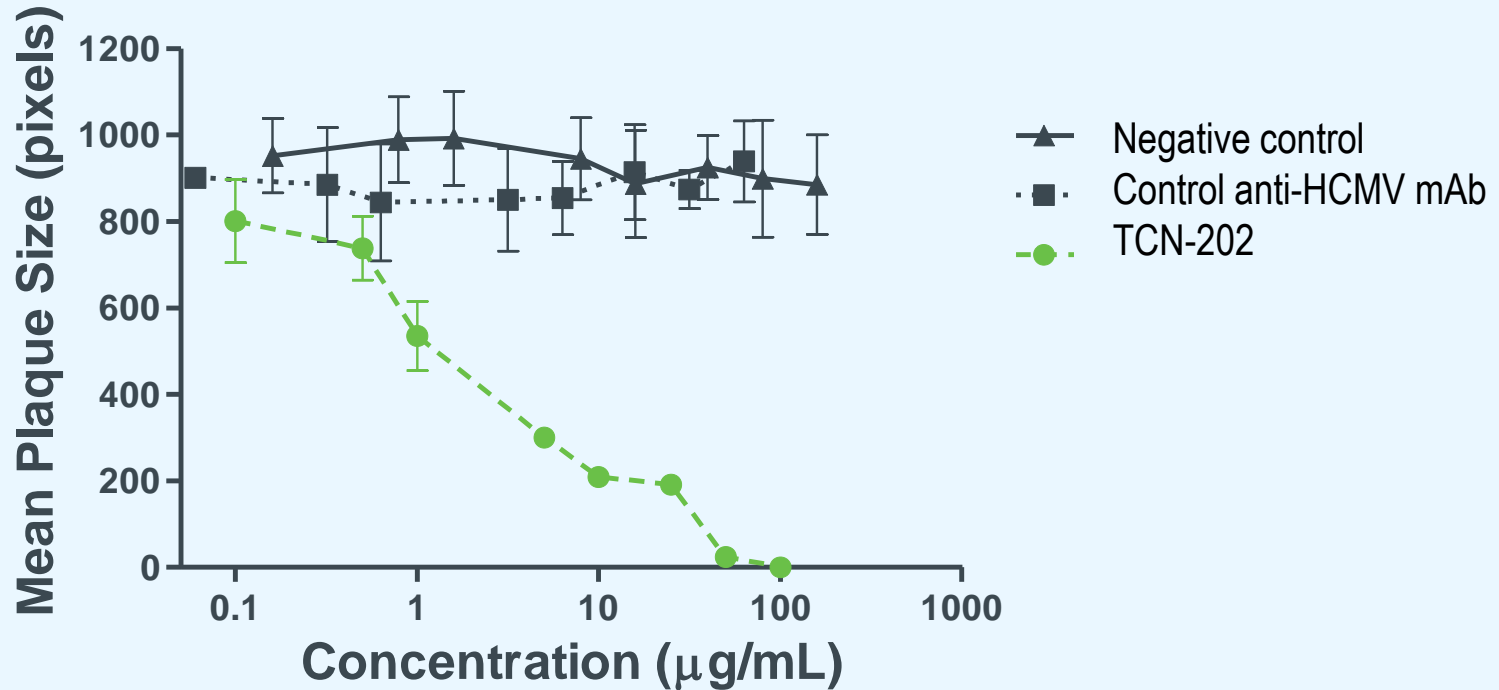
# TCN-202

## A Potent Inhibitor of HCMV

- Broadly reactive human mAb for prevention and treatment of HCMV disease
- MOA: viral neutralization
  - Inhibits critical cell-to-cell infection
  - Nanomolar potency
- Demonstrated efficacy in vitro and in animal model of HCMV disease
- Positive preliminary preclinical safety and manufacturability assessments
- Orphan drug designation granted for congenital infection indication
- Ph 1 clinical trial planned in 2012

# TCN-202

## Inhibits Spread of HCMV



TCN-202 blocks cell penetration and cell-to-cell spread of HCMV  
important for therapeutic efficacy

# Human Rhinovirus bNAb Discovery Program

Addressing Severe Complications Caused by the Common Cold

# HRV – A Severe Threat in Chronic Respiratory Diseases

## Therapeutic Rationale

- High-risk group – Chronic respiratory disease (Asthma, COPD, CF)
  - Acute exacerbation of disease
  - Increased number of hospitalizations
  - Major cause of morbidity and mortality
- HRV-C infection in children recognized as new challenge
  - Frequently associated with more severe lower tract respiratory infection
  - Can direct infant immune system to develop asthma
  - Strong correlation with asthma exacerbations and febrile wheeze
  - HRV-C occurrence: 28-52% in respiratory disease
- No effective preventive or therapeutic treatment

# Prophylaxis of HRV Infection

## Clinical Opportunities in Asthma Indication

- Peak season well defined
  - Prior to commencement of school year
- Likelihood of developing asthma in childhood can be reduced
  - HRV infection is principal risk factor by age 3
- HRV occurrence higher than RSV
  - Several reports of hospitalized children due to HRV infection
- Precedence for use of mAb (e.g. omalizumab) in prevention and prophylaxis of asthma
- Existing unmet need in asthma exacerbation triggered by HRV
  - Patients unresponsive to SOC including inhalers, omalizumab, etc.
  - Anti-HRV mAb will provide additional option

# TCN Anti-HRV bNAbs

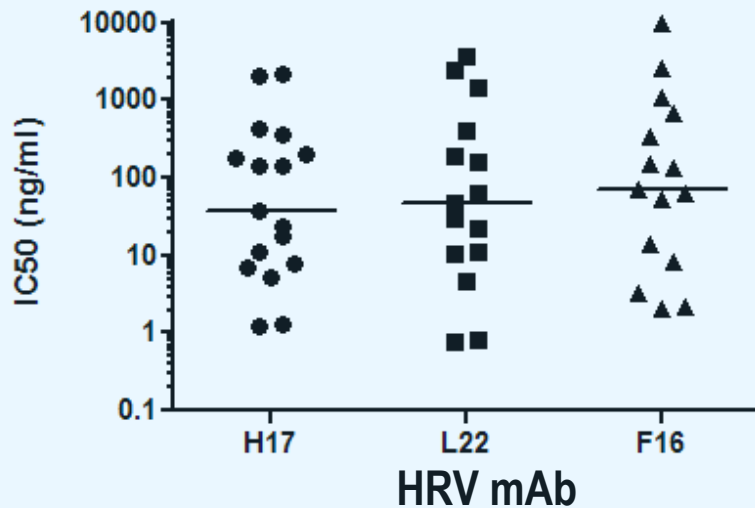
## Potent Clade A Neutralizers and Broad Binders Identified

- Develop cross-serotype neutralizing human antibodies – bNAbs
  - Prevent HRV infection in patients at high risk
  - Minimize acute exacerbations of asthma and COPD
- MOA of therapeutic candidates
  - Mono-therapy with bNAb
  - Cocktail of cross-serotype mAbs to neutralize majority of viral strains
- Discovery program ongoing
  - Identified broad clade A neutralizer and broad cross-clade A & B binder
  - Expanded program to discover broad HRV clade C neutralizer

# In Vitro Efficacy of mAbs Discovered at Theraclone

## Anti-HRV mAbs Neutralize Cross-Serotype

Potency of neutralizers tested against clade A virus



Median IC<sub>50</sub>: 38 ng/ml 47ng/ml 73ng/ml

Additive breadth of neutralization

22 clade A serotypes

%	H17	L22	F16
H17	73	77	82
L22		68	77
F16			64

Cocktail of up to 3 mAbs

> 80% clade A major group

# Upcoming Milestones

Date	Milestone
2012	Deliver lead candidates to existing corporate partners Establish strategic alliances to accelerate: influenza, HCMV and discovery programs
H1 2012	Report Phase 1 trial results for TCN-032 (Influenza) File IND for TCN-202 (HCMV)
H2 2012	Initiate viral challenge study for TCN-032 Start Phase 1 trial for TCN-202

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