Top Trends to Watch Shaping the Future of Pharma and Biotech
台灣生技與製藥：大趨勢看未來

Development of Biologic Therapeutics for Critical Diseases
A Success Story of a Local Biopharmaceutical Leader

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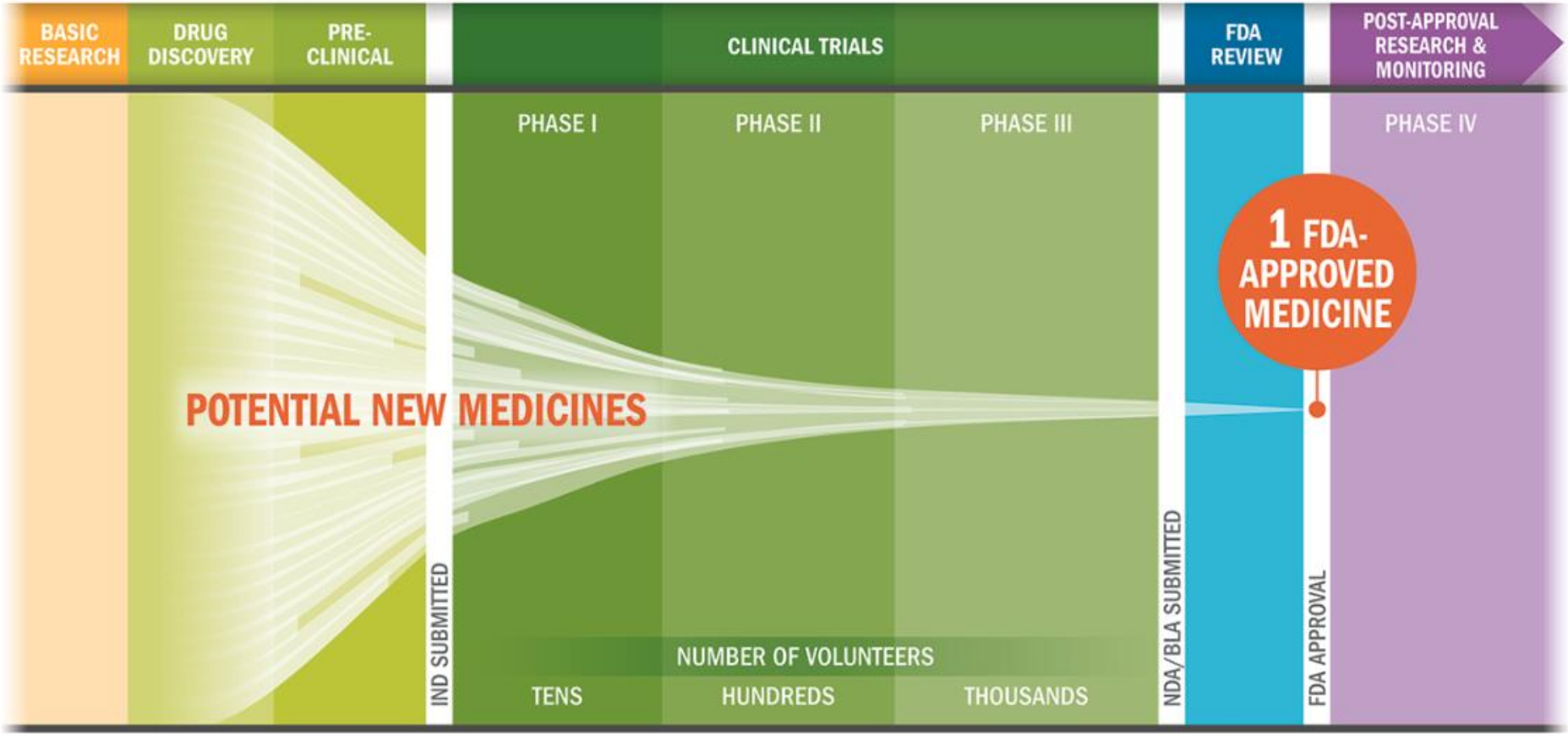
THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of $2.6 billion.* Less than 12% of the candidate medicines that make it into Phase I clinical trials will be approved by the FDA.



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US ResourcesForYou/Consumers/UCM284393.pdf (accessed Jan. 20, 2015).

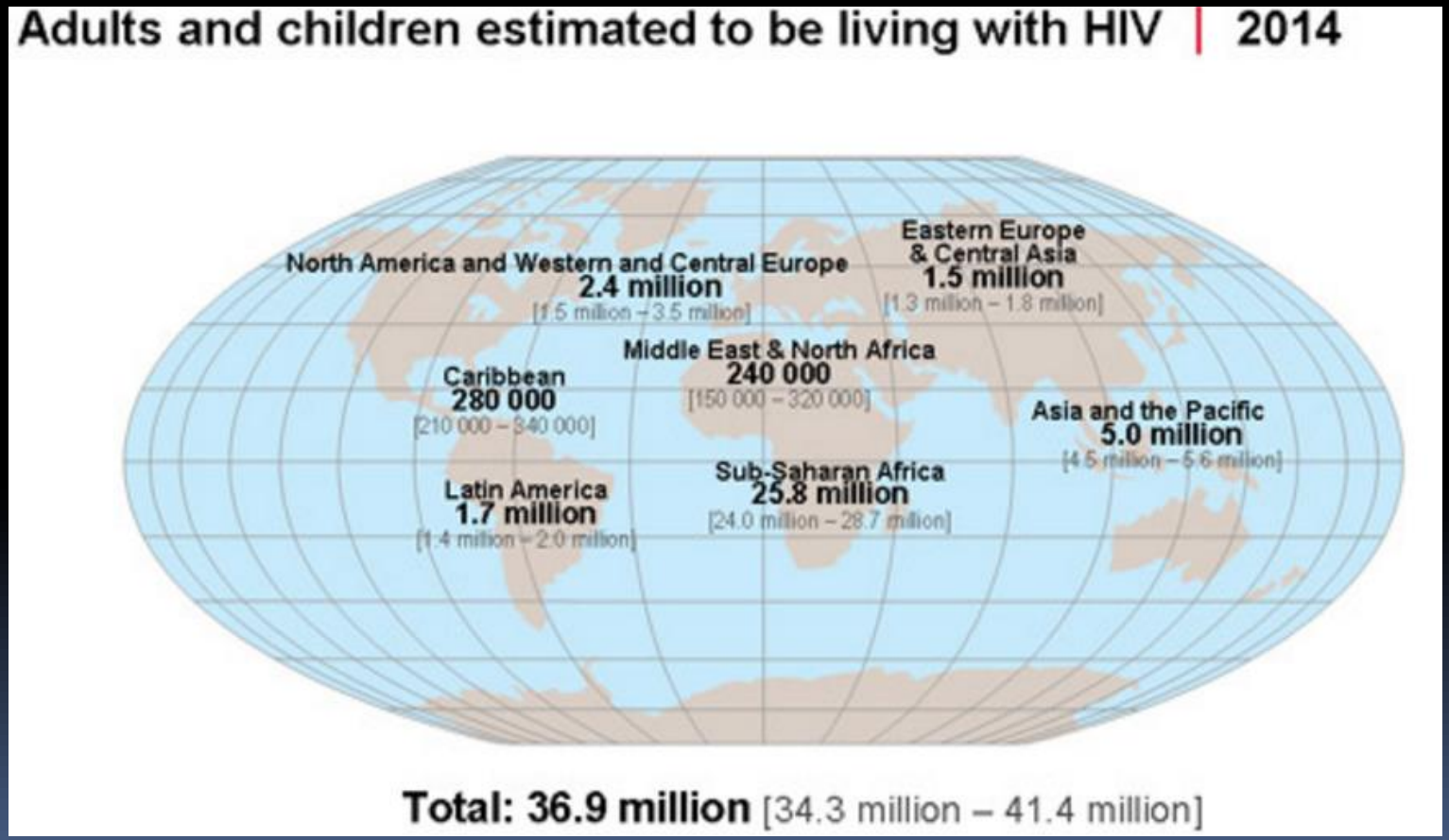
graphic/the-biopharmaceutical-research-and-development-process#

TaiMed Biologics Mission and Business Model

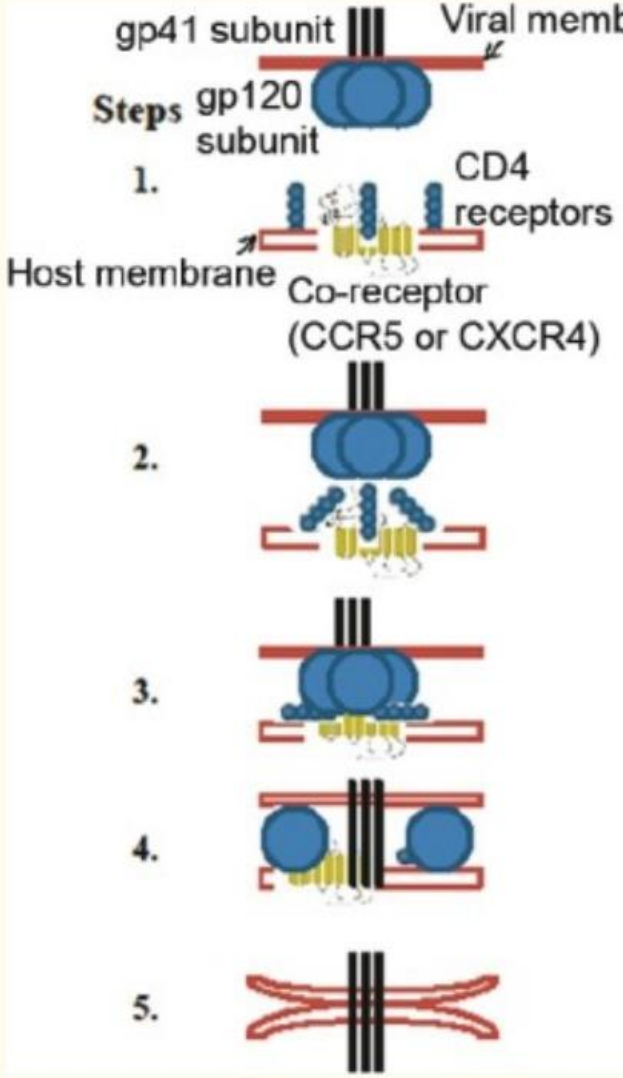
- TaiMed is committed to finding safe and effective treatments for those patients suffering from HIV/AIDS
- Development led by science
- Develop licensed assets from bench through the clinic
- Smart business development
  - In-license quality molecules
  - Outlicense / codevelop with the right partners
- Return value to our investors

HIV Patients Distribution-Worldwide

Over 35 million people infected with HIV worldwide, and less than 30% receive treatment



Multistep process of viral entry pathway



Envelope glycoprotein on the surface of HIV-1 consist of two subunits - gp120, external subunit responsible for binding to target cell receptors (CD4) and gp41, trans-membrane subunit which catalyses fusion reaction.

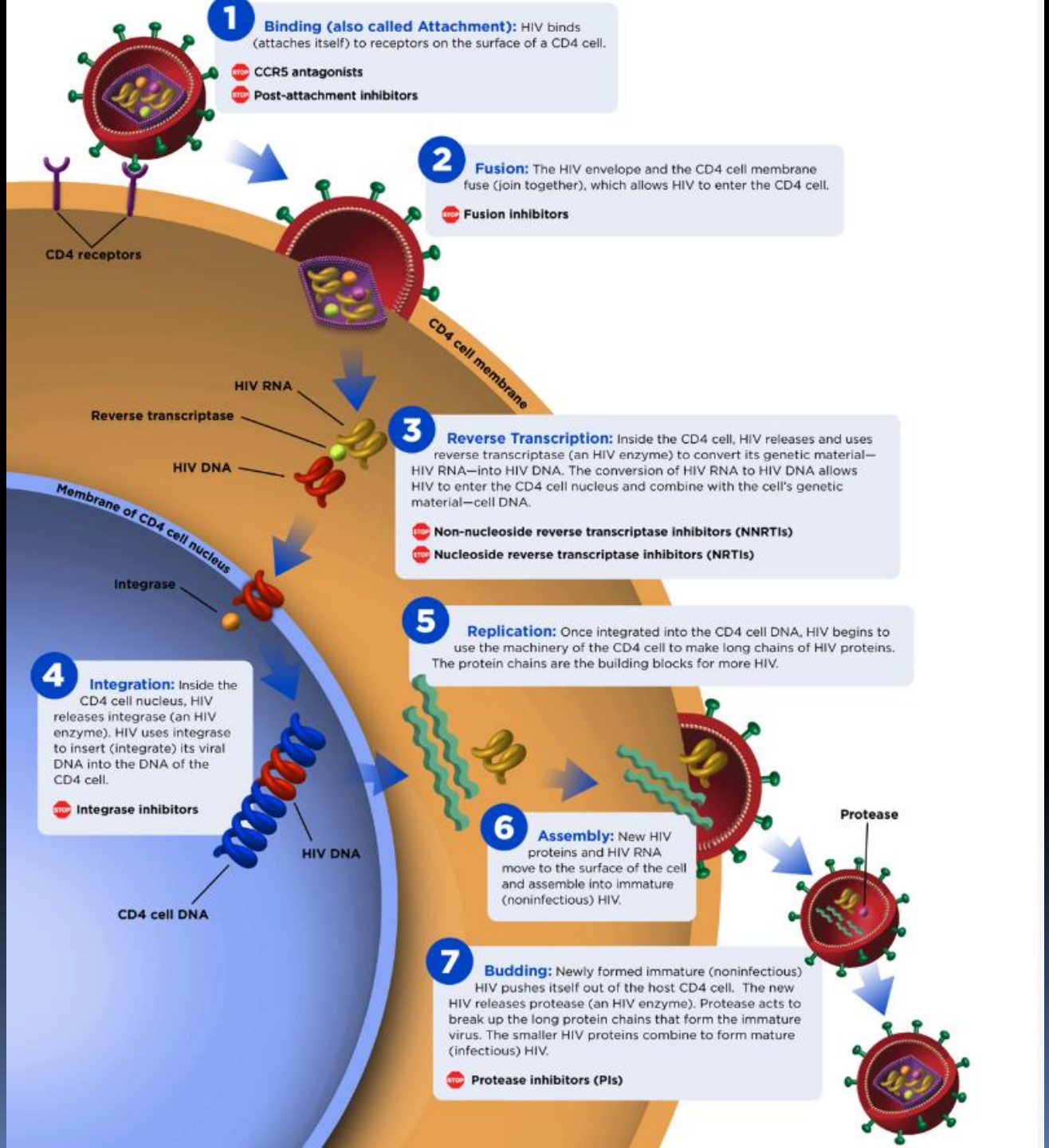
The gp120 subunit first binds with CD4 receptor and undergoes a conformational change exposing structural elements which bind to co-receptors (CCR5 or CXCR4, according to the tropism)

Binding of gp120 to the co-receptor.

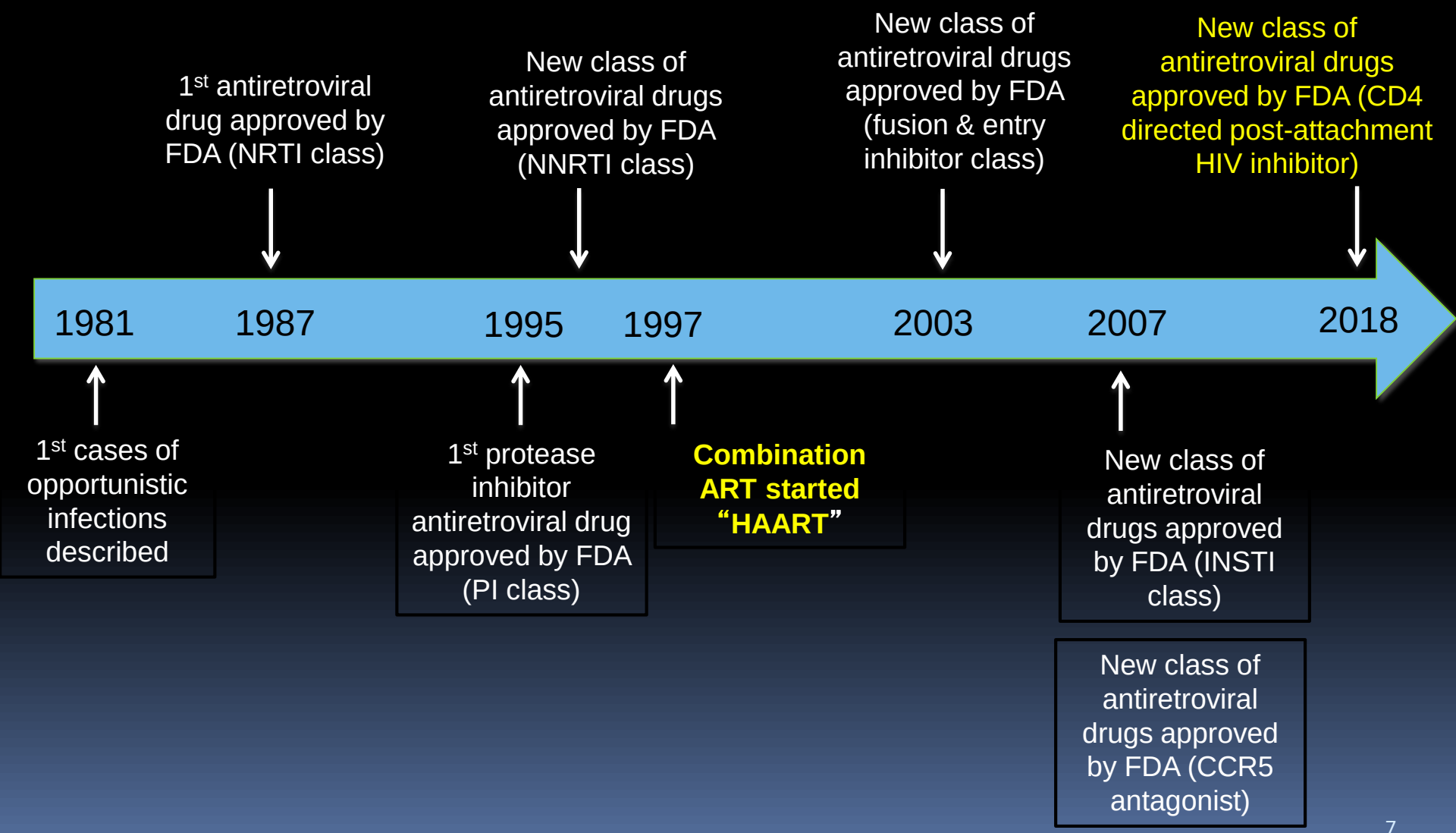
Insertion of gp41 in the cell membrane of the host cell.

Fusion of cell membrane of host cell and viral membrane

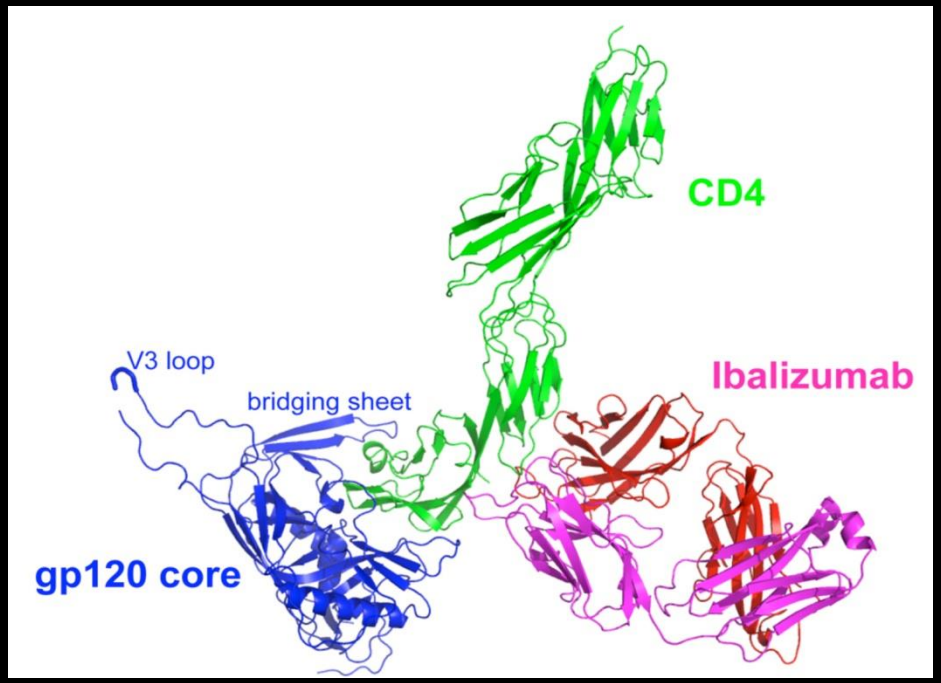
Indian Jour Pharma 2012, 44, 288

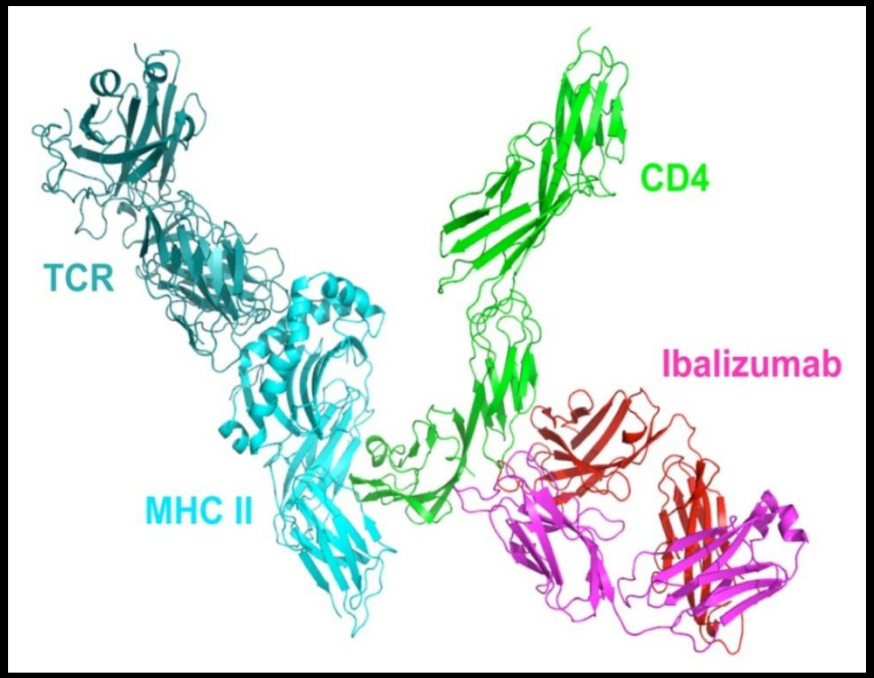

1 Binding (also called Attachment): HIV binds (attaches itself) to receptors on the surface of a CD4 cell.
CCR5 antagonists
Post-attachment inhibitors
CD4 receptors
2 Fusion: The HIV envelope and the CD4 cell membrane fuse (join together), which allows HIV to enter the CD4 cell.
Fusion inhibitors
CD4 cell membrane
HIV RNA
Reverse transcriptase
HIV DNA
3 Reverse Transcription: Inside the CD4 cell, HIV releases and uses reverse transcriptase (an HIV enzyme) to convert its genetic material—HIV RNA—into HIV DNA. The conversion of HIV RNA to HIV DNA allows HIV to enter the CD4 cell nucleus and combine with the cell's genetic material—cell DNA.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
Nucleoside reverse transcriptase inhibitors (NRTIs)
Membrane of CD4 cell nucleus
Integrase
5 Replication: Once integrated into the CD4 cell DNA, HIV begins to use the machinery of the CD4 cell to make long chains of HIV proteins. The protein chains are the building blocks for more HIV.
4 Integration: Inside the CD4 cell nucleus, HIV releases integrase (an HIV enzyme). HIV uses integrase to insert (integrate) its viral DNA into the DNA of the CD4 cell.
Integrase inhibitors
HIV DNA
CD4 cell DNA
6 Assembly: New HIV proteins and HIV RNA move to the surface of the cell and assemble into immature (noninfectious) HIV.
Protease
7 Budding: Newly formed immature (noninfectious) HIV pushes itself out of the host CD4 cell. The new HIV releases protease (an HIV enzyme). Protease acts to break up the long protein chains that form the immature virus. The smaller HIV proteins combine to form mature (infectious) HIV.
Protease inhibitors (PIs)

History of Antiretroviral Therapy



Ibalizumab Epitope
Distinct the gp120 and MHC-II Binding Sites





M. Freeman, et al., 2010

- 3-D structure model of CD4 interaction with gp120 and MHC II (major histocompatibility complex II) -TCR in the presence of Ibalizumab
  - Interference with CD4-mediated immune functions has not been observed

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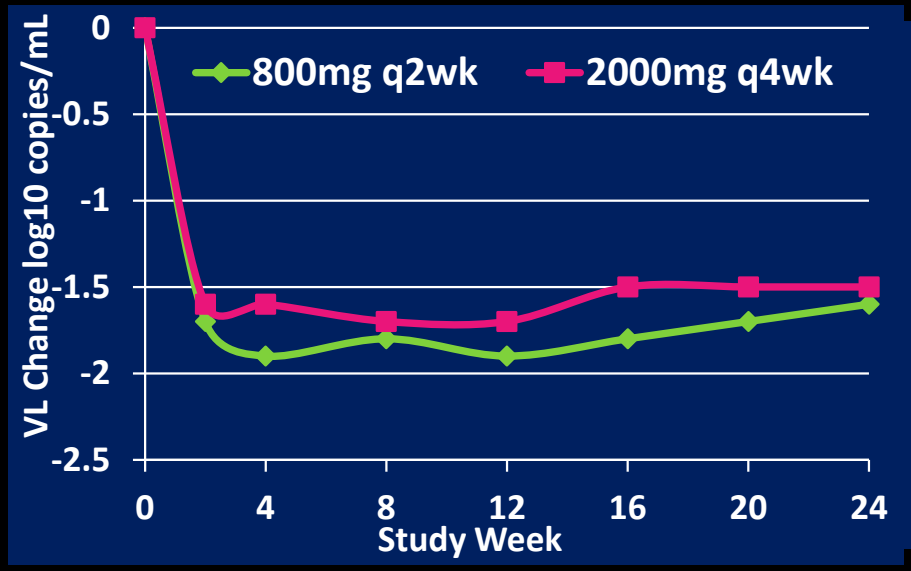
Ibalizumab is broad and potent in blocking HIV in vitro

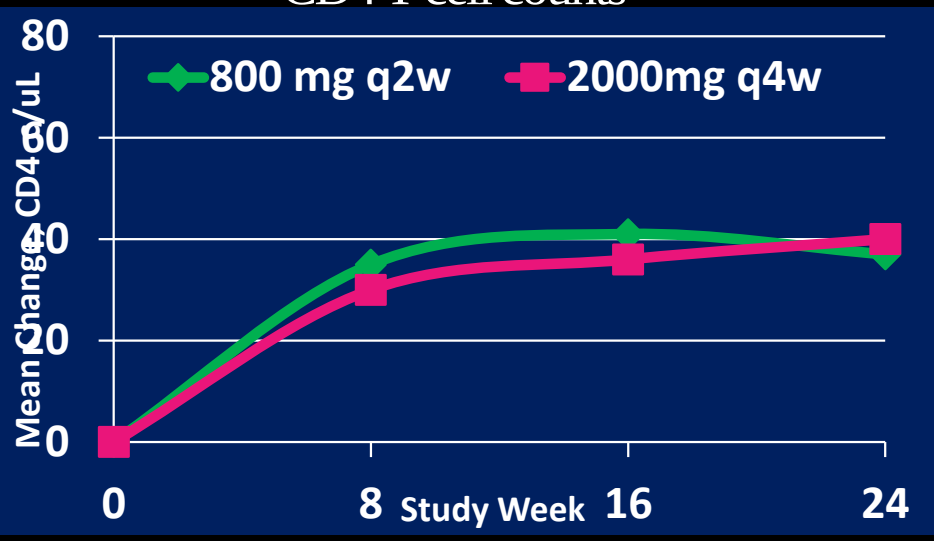
VIRUS	CLADE	TROPISM	IC_{50} (μg/mL)
US1	B	R5	0.0004
91/US/056	B	R5	0.001
92/US/717	B	R5	0.0004
JR-CSF	B	R5	0.162
ADA-M	B	R5	0.027
HIV89.6	B	R5/X4	0.048
92/RW/009	A	R5/X4	0.001
ZB20	C	R5	0.0006
92/UG/035	D	R5	0.008
CM235	E	R5	0.005
CM246	E	R5	0.009
42368	E	R5/X4	0.003
BCF03	O	X4	0.008

Ibalizumab IV Phase IIb -Summary of Efficacy Data

viral load



CD4 T cell counts



800 mg q2wk: -1.6 log 10 copies/mL

2000 mg q4wk, -1.5 log 10 copies/mL

patients with 1 log reduction

800mg q2wk: 63%;

2000mg q4wk: 57%

patients with <50 copies/mL at Week 24
800 mg q2wk: 44%
2000mg q4wk: 28%

Mean change in $CD4^+$ T-cells at Week 24

800 mg q2wk: +37 cells/µL

2000 mg q4wk :+40 cells/µL

Twenty-six percent (26%) of patients had baseline CD4 counts <20 cells/µL; reduced to 12 % at Week 24

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Differences between arms the were not statistically significant
ITT-MEF Intent to treat population with missing treated as failure

Milestones
Ibalizumab (TMB-355)

- FDA approval-3/6/2018
- Pre-Approval Inspection – 7/17/2017
- Granted US FDA priority review- 7/1/2017
- Completed BLA submission to US FDA- 5/3/2017
- Completed Phase III trial – 11/2016 (US, TW)
- Granted US FDA awards the orphan drug trials 500K for one year – 10/2016
- Granted US FDA breakthrough designation therapy for MDR patients in IV dosage form – 2/2015
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- Completed Phase II b -2011 (US, TW)

Ibalizumab -Challenges and Niche

Challenges

- Cost of a standard Phase III trial (partner with big pharma)
- Cost of production of ibalizumab

Niche

- Understanding the needs for multidrug resistant patients and advocacy groups
- Novel mechanism (first in class)
- First antibody drug in treatment of HIV patients
- First long-acting injectable drugs in HIV therapy

- Orphan indication may lead to smaller Phase III trial

Orphan Drug Designation

- Criteria
  - Disease prevalence must be under 200,000
- Advantages include
  - 50% tax credit on the cost of clinical trials in the US
  - 7 year marketing exclusivity
  - Fast-track reviews for registrational filings
  - More flexibility with trial design
  - Possibly fewer trials needed, smaller trials
  - User fee waivers
  - Grant funding for clinical trials up to $500,000 per year

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Breakthrough Therapy

U.S. Food and Drug Administration
Protecting and Promoting Public Health

Breakthrough Therapy Designation

New designation created by the Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144 (July 2012)

General Criteria

- Serious condition
- "Preliminary clinical evidence" indicates that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints

Assistance provided by FDA

- Intensive guidance on efficient drug development
- Organizational commitment
- Eligible for rolling review

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Breakthrough Therapy Designation

- Type of FDA assistance (as appropriate) for drugs with breakthrough therapy designation (set out in statute, section 902 FDASIA):
  - holding meetings with the sponsor and the review team throughout the development of the drug
  - providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable
  - taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment

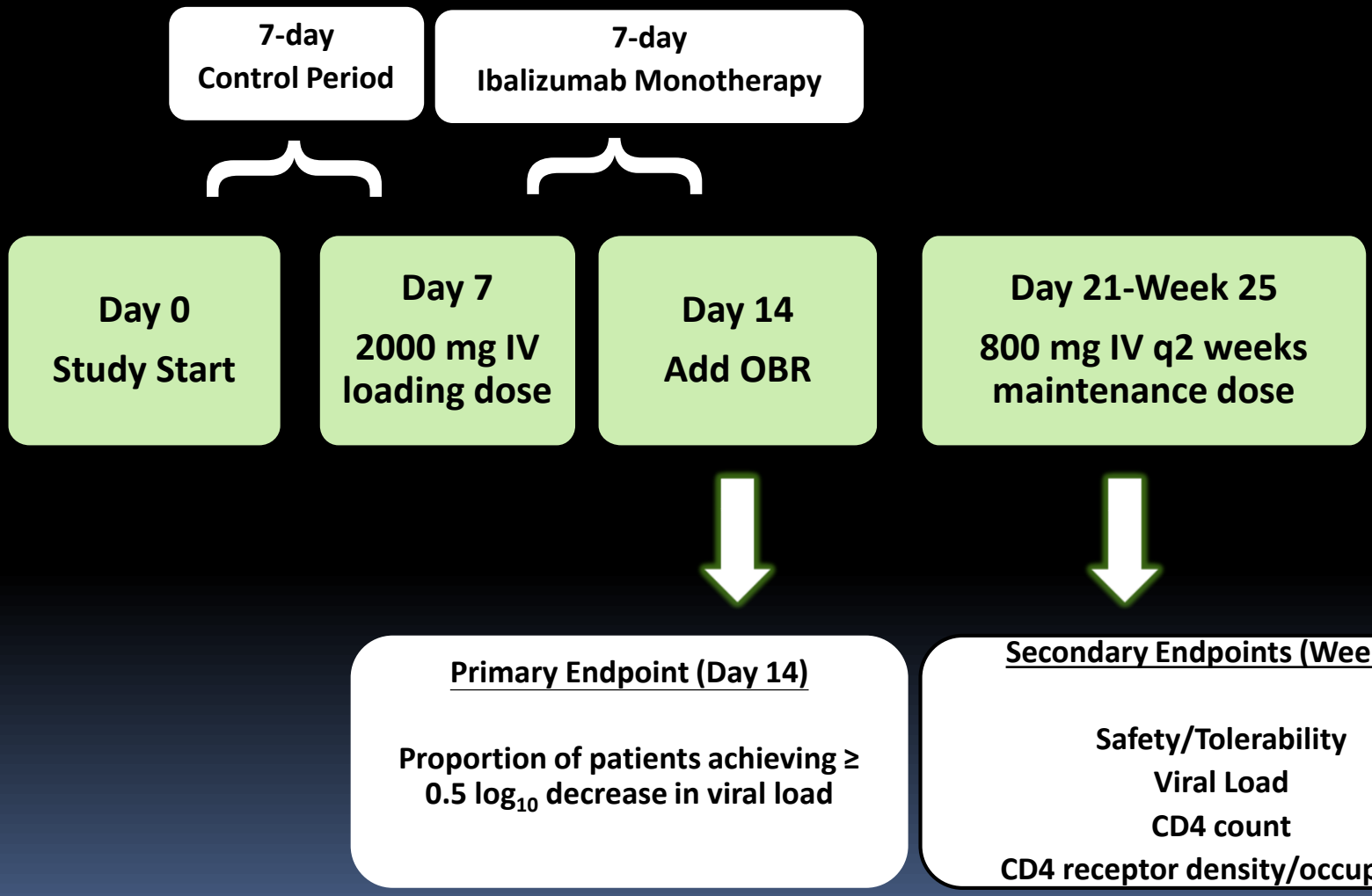
Breakthrough Therapy

U.S. Food and Drug Administration
Protecting and Promoting Public Health

Breakthrough Therapy Designation

- Type of FDA assistance continued:
  - assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the cross-discipline members of the review team (i.e., clinical, pharmacology-toxicology, chemistry, manufacturing and control, compliance) for coordinated internal interactions and communications with the sponsor through the review division's Regulatory Health Project Manager
  - involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review

TMB-301: Phase III Open-Label Study
Registrational Study



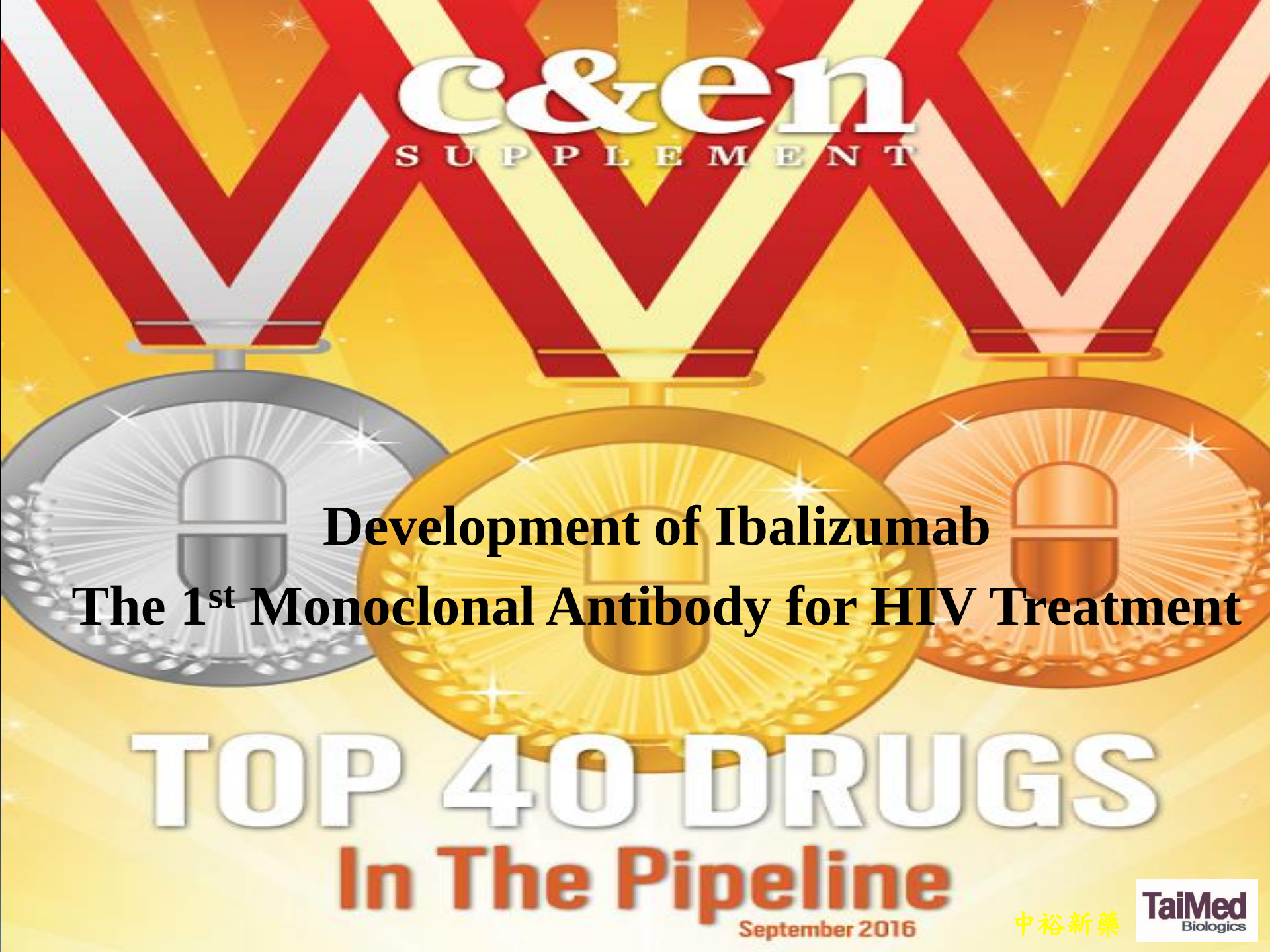
Phase III Results:

Achieved the Primary Endpoint

- 83% with $\geq$ 0.5 $\log_{10}$ in viral load reduction after 7 days.
- Mean/median viral load reduction of 1.1 $\log_{10}$ after 7 days.
    - (Presented these results at ID week 10/29/2016)

Significant Reduction of Viral Load over 24 Weeks

- Mean reduction in viral load was 1.6 $\log_{10}$
- 48% of patients had a reduction > 2.0 $\log_{10}$
- 43% of patients with undetectable viral load (HIV-1 <50 copies/mL) and mean viral load reduction was 3.1 $\log_{10}$
- The safety results in this Phase III trial are consistent with the Phase IIb study
    - (Presented to CROI 2/14/2017)



Development of Ibalizumab

The 1st Monoclonal Antibody for HIV Treatment

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Marketing Partner Strategy

- Shift from Big pharma to specialty pharma due to orphan designation
- Specialty pharma focus on HIV, selling products share the same doctors and potential patients with ibalizumab
- Specialty pharma offer badly needed focus in pushing new products to market
- Deal terms with higher back end, higher profit sharing

Theratechnologies marketing deal in March 2016

(only one product, Egrifta, on market)

Committed to HIV Drug Development with a Solid Pipeline

TMB-607

- Protease inhibitor
- Phase I clinical trial underway (IND sponsored by Temple University)

TMB-365

- Ibalizumab-based, IgG1-scaffold, also blocks domain 2
- Broader, wider viral coverage range and higher, greater anti-infectivity against HIV
- FcRn, LM52 glycan modifications
- Phase I start Q3 2018

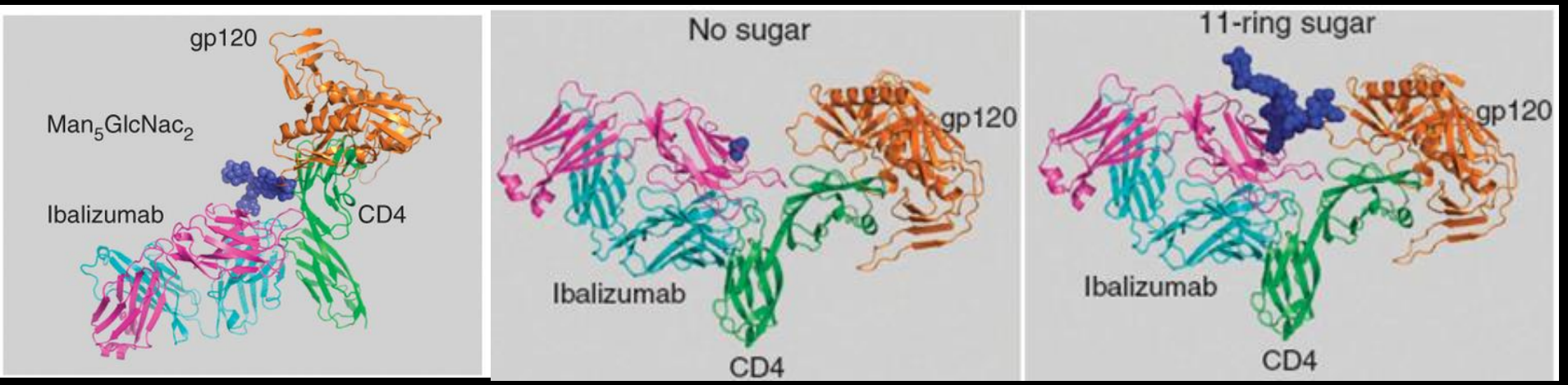
TMB – Bispecific

- Bispecific neutralizing antibody targets two different antigens
- One targets CD4 like ibalizumab while the other targets gp41
- Currently in preclinical development

TMB – ADC

- Antibody-drug conjugate
- Tripartite drugs comprising a target-specific mAb conjugated to a potent HDAC inhibitor via a stable linker
- Currently in discovery

Reasons for HIV Resistance to Ibalizumab Strategy to Improves Activity



- Reasonable to "refilling" the steric congestion with glycans at proper position near gp120 V5 region and ibalizumab light chain
- Modified ibalizumab has a glycan added at aa52 of the mAb light chain
- The CD4-binding activity of LM52 is very similar to that of ibalizumab

- Pace et al, JAIDS 2013; Song et al, Nature Biotech 2013

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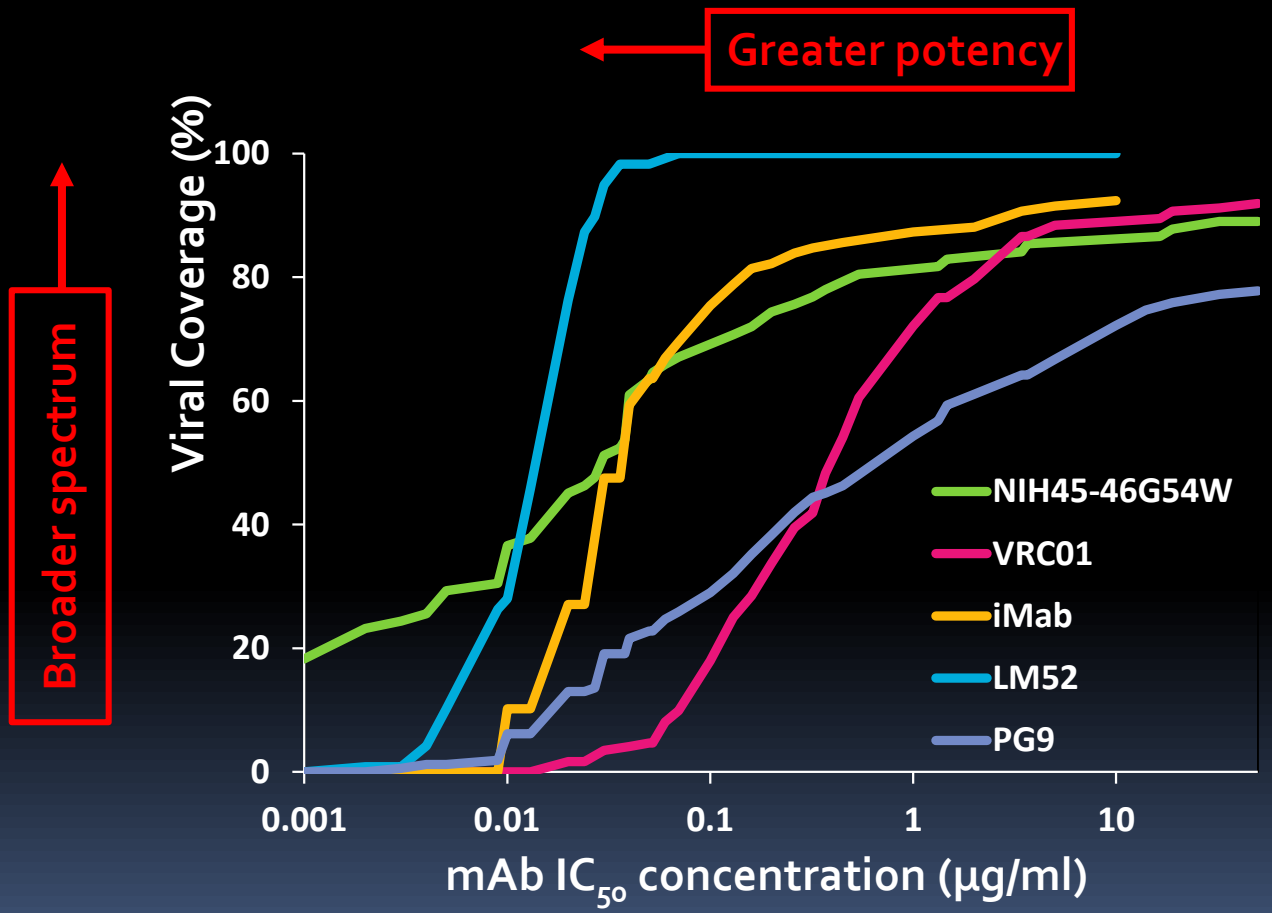
2nd- Generation of Ibalizumab (LM52) Enhanced Breadth and Potency against HIV



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Summary

- Strategy (therapeutic area)
- Pipeline
- Cash position/Funding raising and Revenue generation
- Marketing strategy

- Last but not least
  - Highly trained and disciplined employee
  - Government incentive policy

Acknowledgement

TaiMed Biologics (TW and US)
Dr. James Chang and TMB-355 research team

WuXi Biologics, China
Theratechnologies, Canada

Thanks
Entire clinical trial teams and patients

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Thanks for Your Attention

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