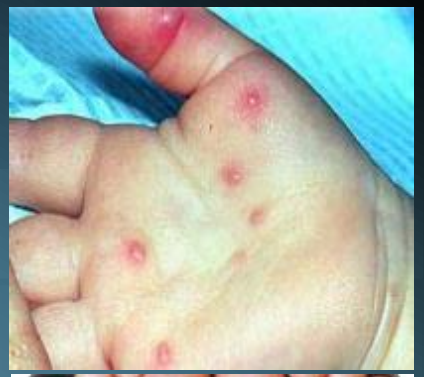
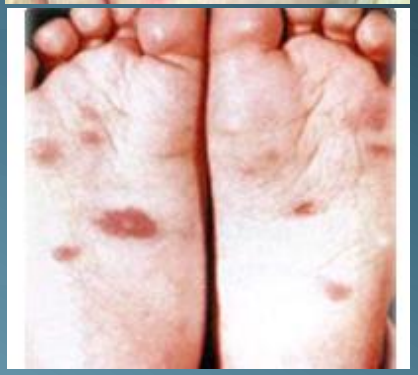
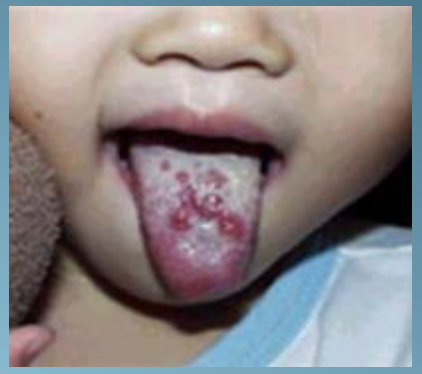
Humanised Anti-EV71 ANTIBODY FOR THE TREATMENT OF HAND, FOOT AND MOUTH DISEASE (HFMD)

BACKGROUND Hand, and Foot and Mouth Disease (HFMD)

- Pathogenesis
  - Enterovirus type 71 (EV71) and Coxsackievirus type 16 (CA16)
  - Infect children under the age of five via fecal-oral transmission
- Symptoms
  - Mild fever first, followed by rash of spots and bumps
- Severe complications
  - Brainstem encephalitis, pulmonary oedema, polio-like paralysis
  - Death







WORLD CLASS SCIENCE: PI and Institute

Prof Zhong Huang

One of top HFMD research laboratories

Strong understanding of HFMD pathogenesis

Access to numerous infectious disease models

Institute Pasteur Shanghai, Chinese Academy of Sciences

Dedicated to infectious diseases that have a great impact on public health in China

Strong understanding of HFMD pathogenesis

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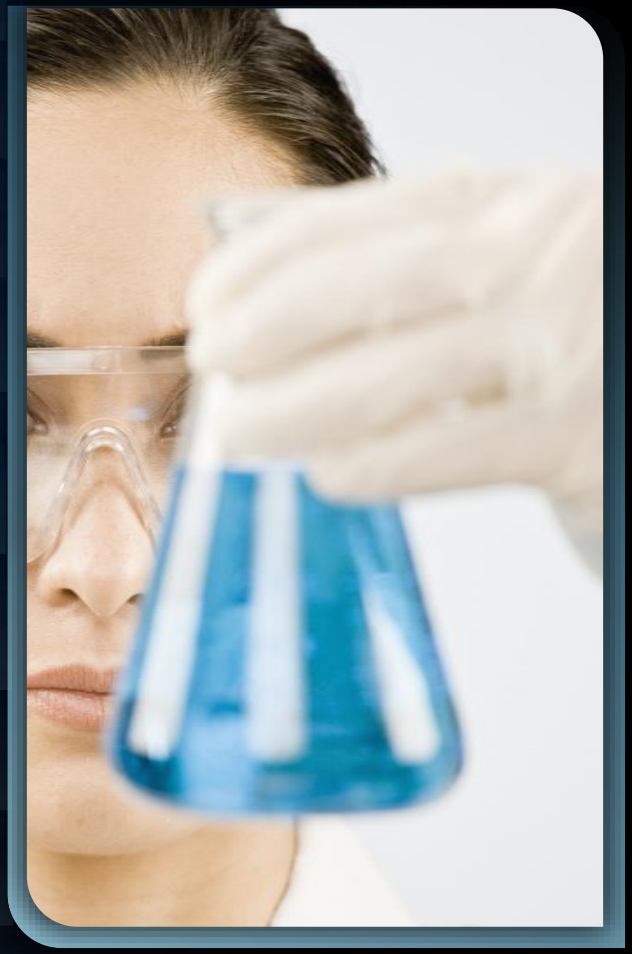


HFMD represents a serious threat to children not only in China but also in many Asia counties

	Incidence		
Territory	2012	2013	2014 – prediction
China	1,920,973	1,651,959	Higher than 2012 ↑
Hong Kong	483	1,620	Similar to 2012 ↓
Macao	1,734	2,145	Similar to 2012 ↓
Japan	66,004	294,535	Similar to 2012 ↓
Singapore	36,371	29,672	Similar to 2012 ↓
Vietnam	/	71,627	Similar to 2012 ↓

EV71 and CA16 are the two major causative agents

- **Both EV71 and CA16 contribute to the recent HFMD outbreaks in China**
- **Humans could be co-infected by both EV71 and CA16 and also carry these two viruses simultaneously**
- **Recombination between CA16 and EV71 has been recently reported**
- **Severe HFMD cases are often associated with EV71 infection**
- **CA16 infection can also cause neurological complication and death**

Yang et al. Virology Journal 2011, 8:508
http://www.virologyj.com/content/8/1/508

VIROLOGY JOURNAL

SHORT REPORT Open Access

Survey of Enterovirus Infections from Hand, Foot and Mouth Disease Outbreak in China, 2009

Fan Yang[†1], Ting Zhang[†1], Yongfeng Hu[†1], Xiaofang Wang[2†], Jiang Du[1], Yufen Li[3], Shaoxia Sun[3], Xiuhua Sun[4], Zhifang Li[3] and Qi Jin[1*]

Province	HMFD cases	Positive for HEV	HEV-71	CV-A16
Beijing	85	75 (88.2%)	38 (50.7%)	31 (41.3%)
Shandong	110	97 (88.2%)	60 (61.9%)	16 (16.5%)
Guangdong	106	94 (88.7%)	36 (38.3%)	55 (58.5%)
Total	301	266 (88.4%)	134 (50.4%)	102 (38.3%)

HEV: Human enterovirus

Anti-EV71 monoclonal antibody (D5)

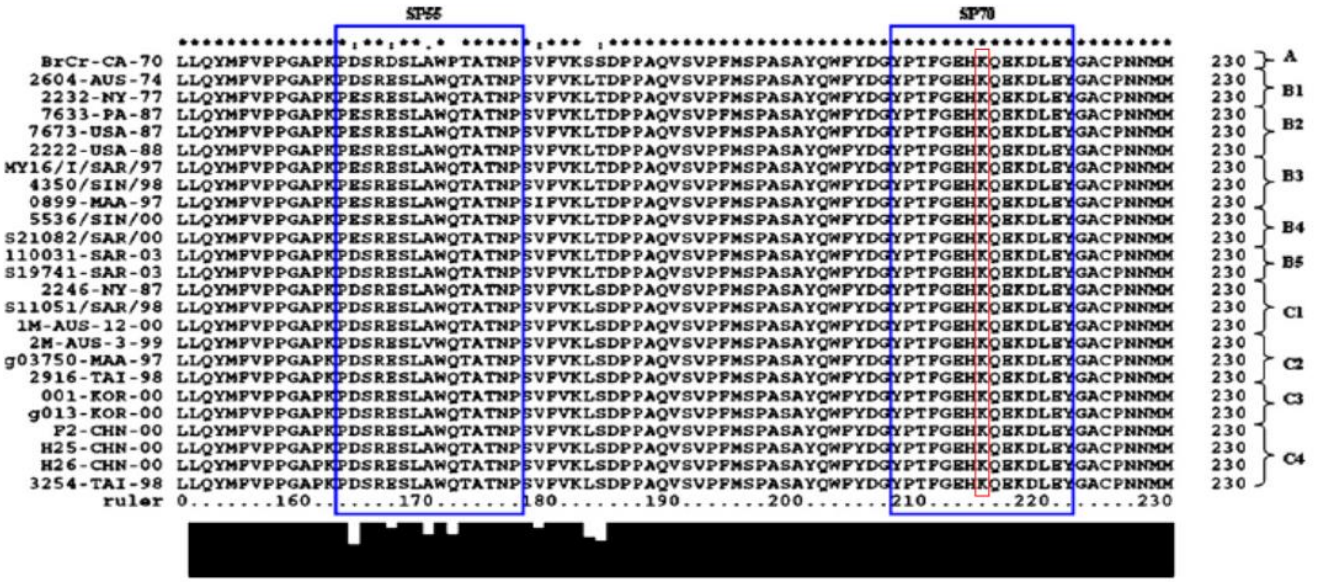
- **Inhibits EV71 binding to SCARB2 and PSGL-1, which are both known virus receptors**
- **Occupying receptor binding sites and blocking virus/receptor interaction**
- **Potently and broadly neutralising a number of clinically relevant EV71 isolates**

	EV71 strain	Lowest concentrations required(ug/ml)	
		D5	C4
(A subtype)	EV71 BrCr	0.625	2.5
(C4 subtype)	EV71 GX08-1	0.625	2.5
	EV71 GX08-2	0.3125	1.25
	EV71 FY2	1.25	10
	EV71 ShZh98	0.625	5
	EV71 FY MAV	o.3125	1.25

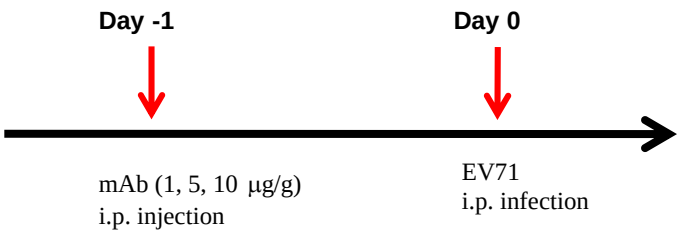
Anti-EV71 monoclonal antibody (D5)

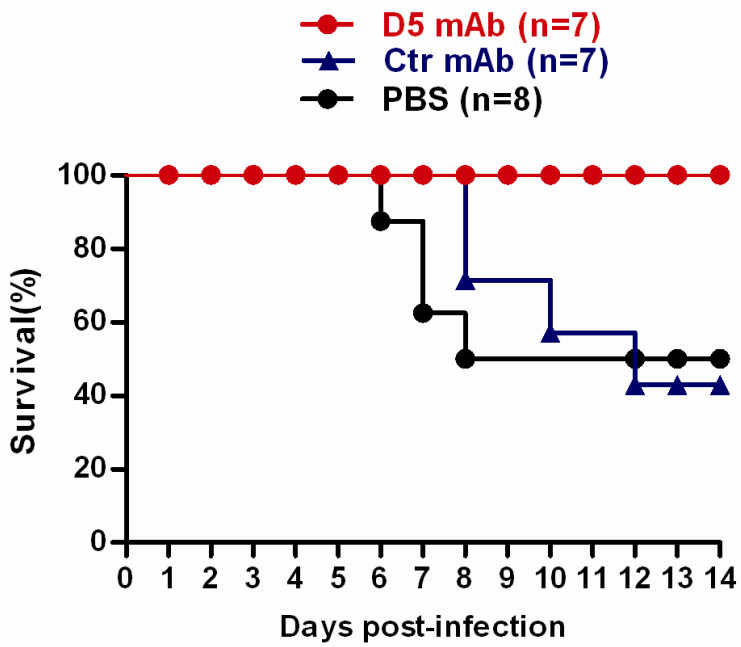
- **The epitope to which D5 binds has been determined and is highly conserved**
- **D5-escape mutants generated and shown to be 'less fit' than the wild-type virus**

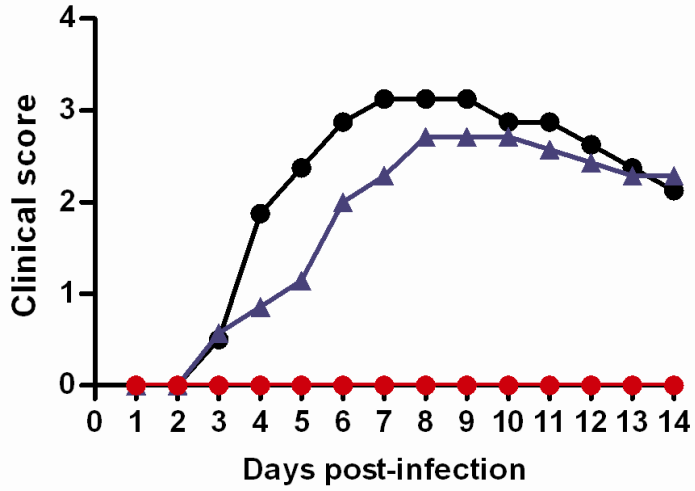
D5 MAb targets highly conserved epitopes



Full prophylactic protection by D5 (from 1mg/kg)

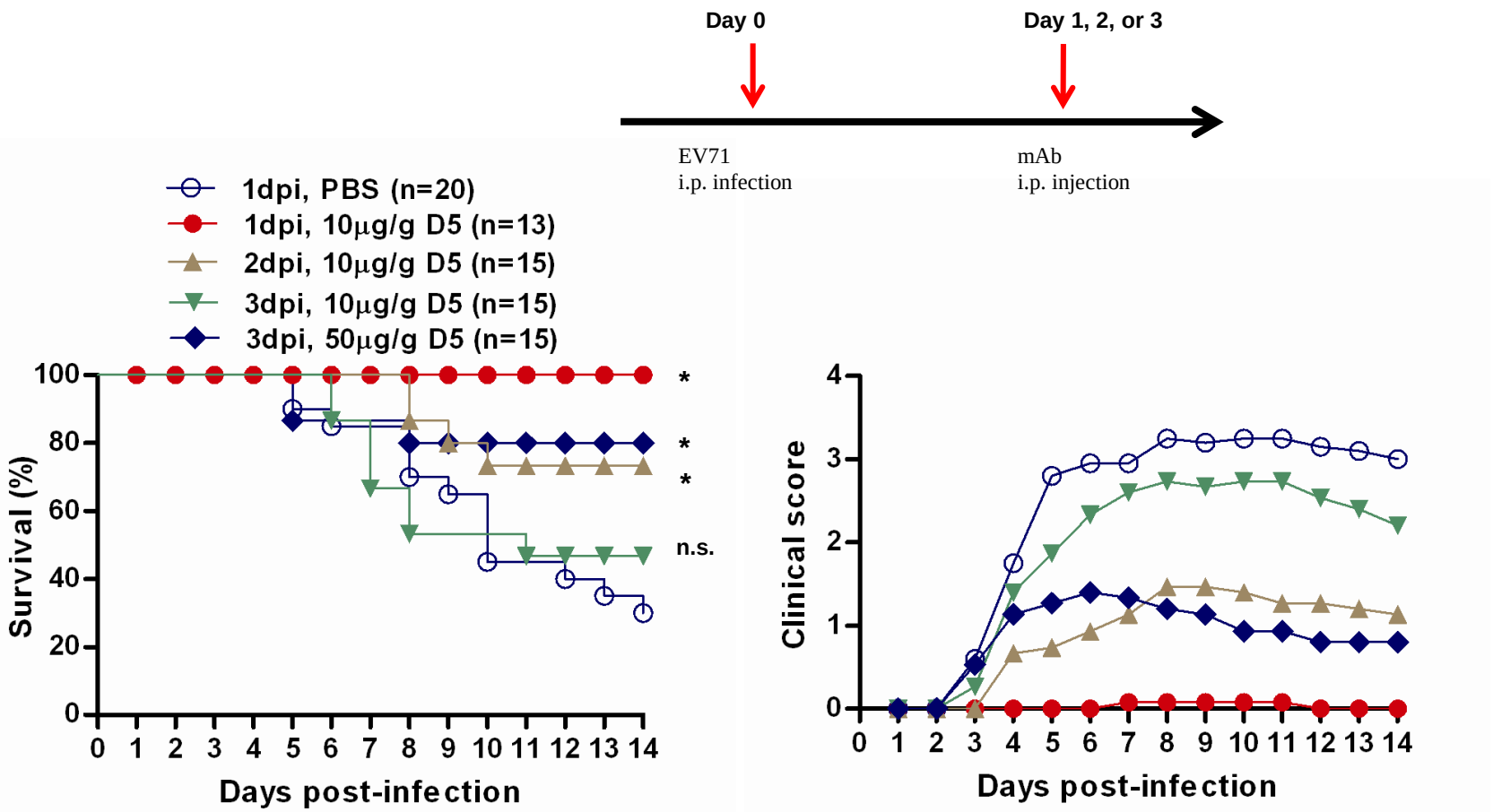






Clinical score grading: 1, reduced mobility; 2, weak limb; 3, paralysis; 4, death.

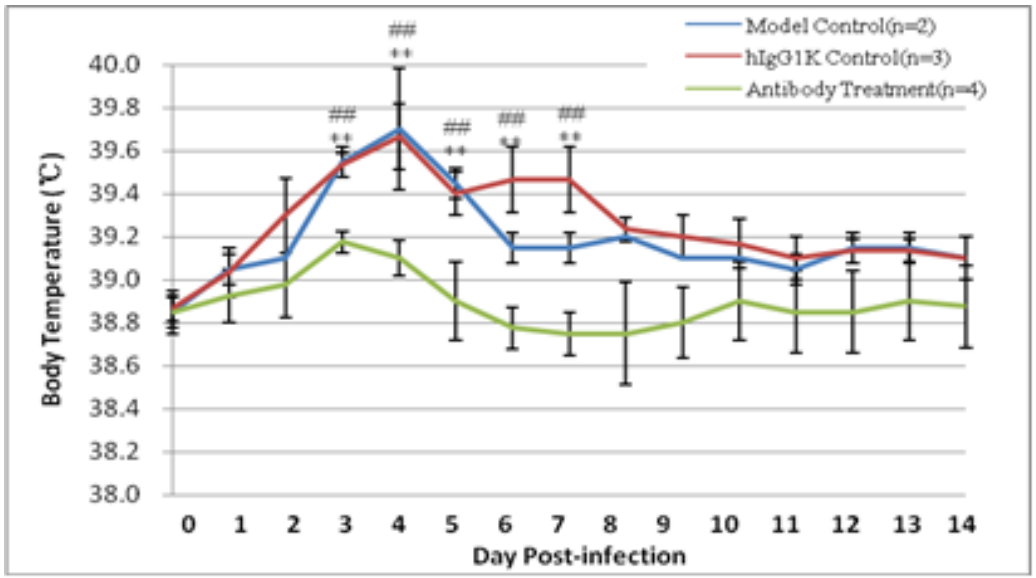
D5 is therapeutically effective (up to 3 dpi)



The experimental design of humanized anti-EV71Mab in clinical strain of EV71 infection of infants of NHP

Groups	i.v	Doses	Concentration	volume	Numbers
Treatment	yes	5 mg/kg	5 mg/ml	1.0 ml/kg	4
Mab control	yes	5 mg/kg	2.7 mg/ml	1.85 ml/kg	3
Un-treated Control	yes	NA	NA	1.0 ml/kg	2

Comparison of changes of body temperature

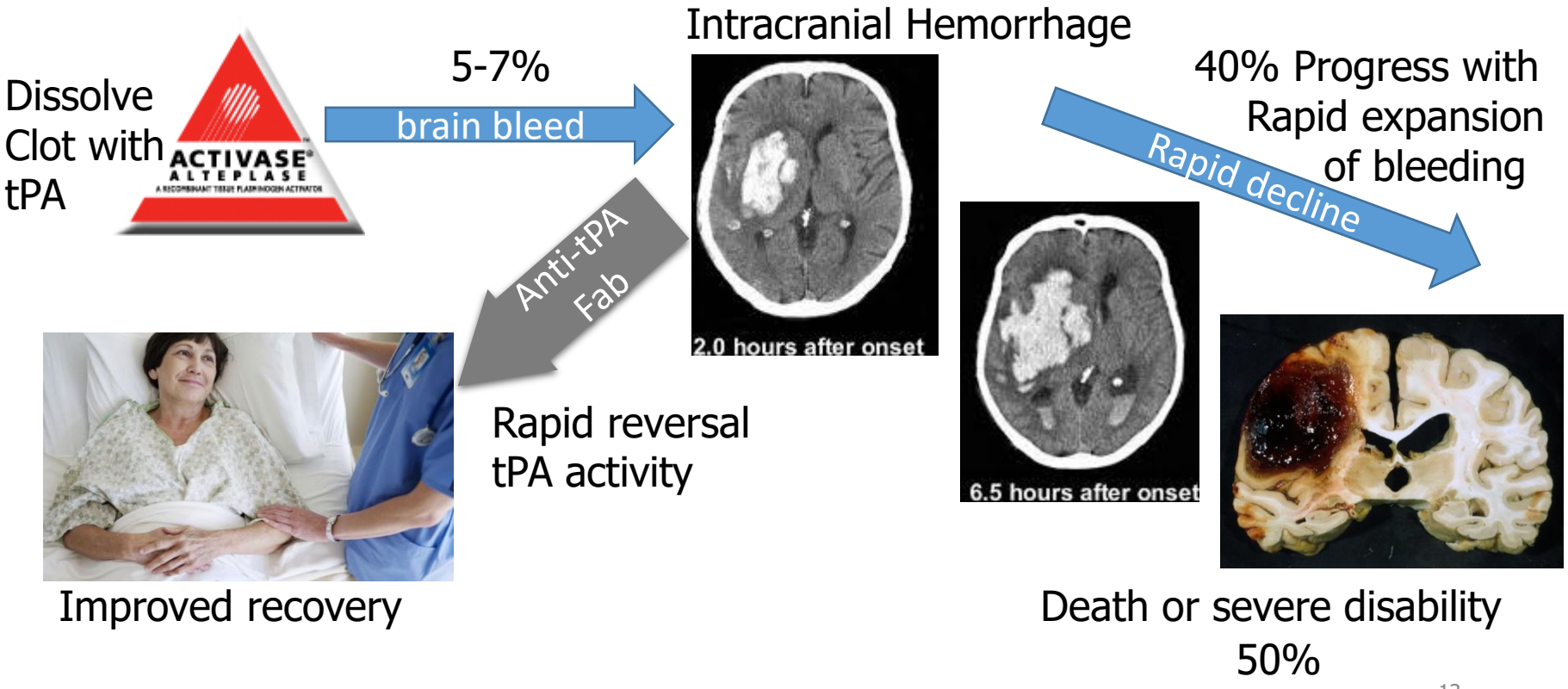


注：治疗组与模型对照组比较，*p<0.05，**p<0.01；治疗组与对照抗体组比较，#p<0.05，##p<0.01.

Anti-tPA antibody Fab opportunity

Technology overview

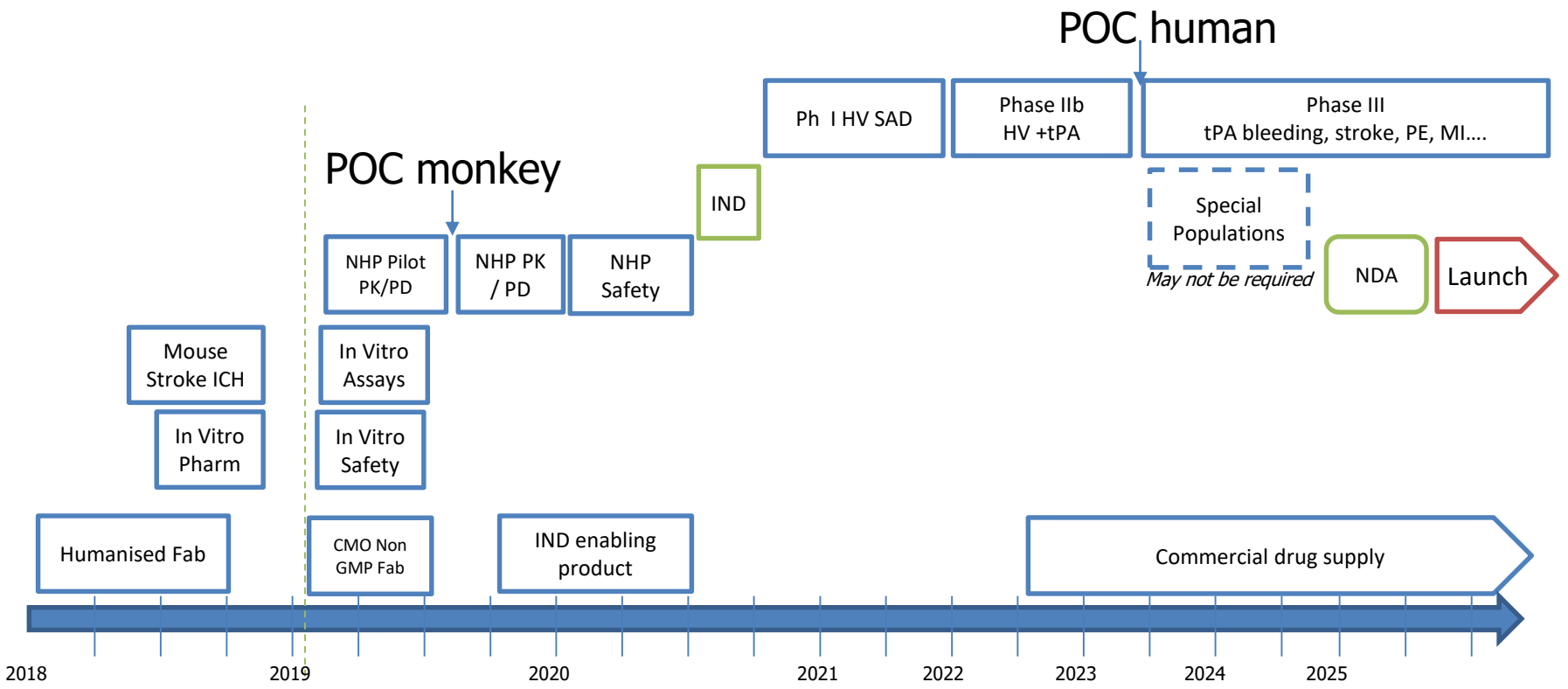
- tPA used to treat stroke, pulmonary embolism, myocardial infarction
- Rates of Intracranial Hemorrhage (ICH) 5-7% with 50% mortality
- Anti-tPA Fab is a monoclonal antibody fragment (Fab) that inhibits tPA
- LifeArc humanised anti-tPA antibody Fab



Accelerated Development Plan

- Follows regulatory pathway of Idarucizumab (Praxbind®)
  - Approved antidote of dabigatran (Direct thrombin inhibitor)
  - Ph1: dabigatran reversal in normal volunteers loaded with drug
  - Pivotal: reversal in dabigatran–treated patients with severe bleeding
  - Others using similar development paths: Andexanet alfa, Ciraparantag
- Precedent for Orphan status, accelerated review
- Regulatory end points are reversal of tPA activity and safety
- Total number patients to file ~350 patients (Ph I to III)

Development Plan and Milestones



Scientific Status

- Efficacy demonstrative in animal model of stroke
  - Experiment repeated with mouse and human antibody
  - Model reflects the human thrombotic stroke
  - Intervention with tPA and antidote reflects clinical practice
- Efficacy relevant to human bleeding after tPA
  - Reduction in bleeding volume
  - Reduction in ischemic volume of stroke
  - Reduction in brain swelling
  - Reduction in systemic bleeding
- Endpoints show a statistically significant difference
  - Reduction in bleeding is likely to translate into human mortality reduction
  - Reduction in infarct and brain swelling are likely to reduce mortality but also improve functional recovery – i.e recovery worth living for
  - Reduction of systemic bleeding in other organs e.g. gut and hence reduce mortality

Current Program Status

- Murine, Chimeric and Humanized Fab
  - have similar Binding and Beneficial Function in the Human Clot Lysis Inhibition & Murine Thromboembolic Stroke Model of tPA-induced ICH
- Human Fab has been developed
  - Similar binding to Activase and TNK and function as original mouse Mab
  - Human clot lysis model shows dose-dependent inhibition
  - Material available for non-GLP NHP study to establish PK and initial PD
  - GMP manufacturing proposals under evaluation
- IP
  - Patent under exclusive license
    - Patent granted in US, under examination in Europe and China
    - Long Patent Life-earliest expiration 2034
  - Patent for newly developed humanized Fab filed

Commercialisation

Market

- tPA use drives the use of anti-tPA
- Anti-tPA will increase use of tPA
- **Launch 2025 Single IV dose**
- Price Global av ~$8,800 /patient
  - Benchmark Novoseven ~$7,300
  - Praxbind ~$3,500
- Patients Rx tPA, ICH/ bleed
  - 2022 540K, 29K
  - 2032 834K, 52K

Peak sales ~$400m

- Higher if antidote needed to be available at bedside when tPA infused
- No new thrombolytic on horizon
- Low dose tPA still 5% ICH in stroke

Valuation

- POC in Humans 2023
  - Value $130m
- Launch 2025
  - Value $800m

Benchmarks

- Praxbind 400Kpts 2020, $1.4bn
  - Apr 2016, Pradaxa (dabigatran) rose 7.4% to €1.3bn, boosted by US approval in October 2015 for its antidote Praxbind
- Portola Ph 2 adexanet $120m JP
- Perosphere Founded 2011
  - Raised 4 rounds $10.9m, Value n/a

Risk mitigation

Risk	Mitigation
Science	Peer Review LifeArc, KOLs EU, US, LA
IP	US patent granted, we own COM patent, have exclusive rights
Clinical Trials	HV to POC, Ph III only 90pts to file, use stroke networks
Regulatory	Recent precedent Praxbind idarucizumab INJECTION 5g approval USA, EU Received Orphan status, Priority review and Accelerated approval
Market	Low dose tPA 5% ICH, no new tPAs or antidotes
Payer	Low budget impact, small fraction total patient Rx cost, HE model
Buyer at POC or Approval	1. Makers of tPA 2. Antidote companies & Speciality pharma 3. Pharma companies with stable cash flow seeking biotech and high margin speciality acquisition