Translational and Early Phase Clinical Research in Singapore

Dr. Danny Soon

Medical Director, D3

2nd ICPOEP

21st November 2015

A*STAR D3

It Starts at the Top

RESEARCH INNOVATION ENTERPRISE COUNCIL

NATIONAL RESEARCH FOUNDATION
PRIME MINISTER'S OFFICE
SINGAPORE
Research . Innovation . Enterprise

The National Research Foundation (NRF) is a dept. within the PM's office, and sets the national direction for R&D by:

- **Developing policies, plans and strategies** for research, innovation and enterprise;
- **Funding initiatives** that strengthen research and scientific capabilities, and achieve economic and national impact;
- **Building up R&D capabilities and capacities** through nurturing our people and attracting foreign researchers and scientists; and
- **Coordinating the research agenda** of different agencies to transform Singapore into a knowledge-intensive, innovative and entrepreneurial economy.

http://www.nrf.gov.sg/about-nrf/national-research-foundation-singapore#sthash.khxwX0im.dpuf

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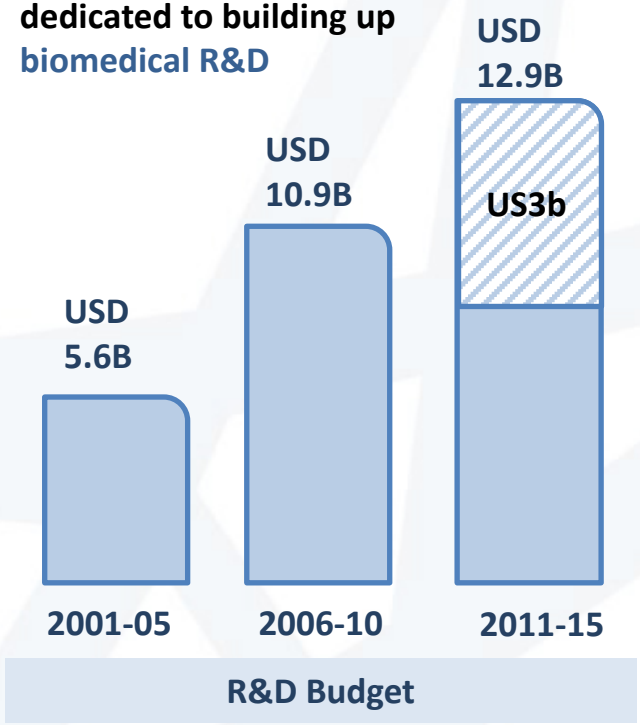
Strong Government Support in R&D

USD 3B Budget dedicated to building up biomedical R&D



1. **USD 100 Million for Translational Clinical Research Programmes**

2. **Focus on Asian Prevalent Diseases**

   METABOLIC DISEASES
   ONCOLOGY
   CARDIOVASCULAR
   EYE DISEASES
   INFECTIOUS DISEASES
   NEUROSCIENCES

3. **Schemes to provide funding for private-public collaborations and clinical trials**

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Funding

Translational and Clinical Research (TCR) Flagship Programme

- TCR Flagship Programmes provide significant levels of funding to build up a critical mass of experienced high-level researchers to facilitate a broader research platform, and increase collaboration both locally and internationally.

- Offers two tiers of funding for over 5 years, to provide existing programmes renewal opportunities and to allow for the funding of new programmes.

- Funds will be drawn from the Research, Innovation and Enterprise (RIE) 2015 Open Collaborative Fund (OCF) budget where S$175M is allocated for the TCR Flagship Programmes.

NMRC National Medical Research Council Singapore

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TCR Flagship Programmes

S/N	Title	Disease area of research	Lead PI (Institution)	Year of award
1	The Singapore Gastric Cancer Consortium – Improving Outcomes for Our Patients	Oncology (gastric cancer)	A/Prof Yeoh Khay Guan (NUS)	2007
2	Vulnerability, Disease Progression, and Treatment in Schizophrenia and Related Psychoses	Neuroscience (schizophrenia)	A/Prof Chong Siow Ann (IMH)	2008
3	Singapore Eye Research Institute TRIOS Programme (Translational Research Innovations in Ocular Surgery)	Eye diseases (glaucoma and corneal diseases)	Prof Donald Tan (SERI)	2008
4	Developmental Pathways to Metabolic Disease	Metabolic disease(developmental origins)	A/Prof Chong Yap Seng (NUS)	2008
5	Scientific Exploration, Translational Research, Operational Evaluation of Disease Prevention and Preventative Measures Through New Treatment Strategies Against Dengue (STOP Dengue)	Infectious diseases (dengue)	A/Prof Leo Yee Sin (TTSH)	2008
6	Genetic Predilection, Epigenetic Change, MicroRNA Profiling and Experimental Therapies in Heart Failure	Cardiovascular diseases (heart failure)	Prof Mark Richards (NUHS)	2013 (Tier-1)
7	Non-Small Cell Lung Cancer: Targeting Cancer Stem Cell and Drug Resistance	Oncology (lung cancer)	A/Prof Tan Eng Huat (NCC)	2013 (Tier-1)
8	Eye Surgery and Innovative Technologies (EyeSITe)	Eye disease (glaucoma and corneal diseases)	Prof Donald Tan (SERI)	2013 (Tier-2)
9	Singapore Gastric Cancer Consortium – Re-defining Gastric Cancer Management	Oncology (gastric cancer)	A/Prof Yeoh Khay Guan (NUHS)	2013 (Tier-2)
10	National Lymphoma Translational Research Program: From Genomics to Therapeutics	Oncology (lymphoma)	A/Prof Lim Soon Thye (NCC)	2014(Tier-1)
11	Singapore Programme of Research to Investigate New approaches – to drug discovery and clinical translation – to deliver improved treatments for Tuberculosis (SPRINT)	Infectious diseases (tuberculosis)	Prof Nicholas Paton (NUHS)	2014 (Tier-1)
12	Developmental pathways to health and disease: metabolic, neurodevelopment and related outcomes	Metabolic disease (developmental origins)	A/Prof Chong Yap Seng (NUHS)	2014 (Tier-2)
13	National Parkinson's Disease Translational Clinical Research Programme	Neuroscience (parkinson's disease)	Prof Tan Eng King (NNI)	2014 (Tier-2)
14	The Eradication of Chronic Hepatitis B	Infectious diseases (hepatitis B)	Prof Lim Seng Gee (NUHS)	2015 (Tier-2)

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Niche Capabilities

IMUs

Early-phase Clinical Trial Units

NUHS National University Health System

SingHealth

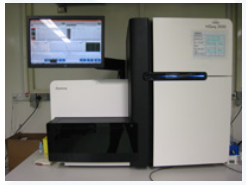
Changi General Hospital SingHealth

Imaging

CLINICAL IMAGING RESEARCH CENTRE SINGAPORE

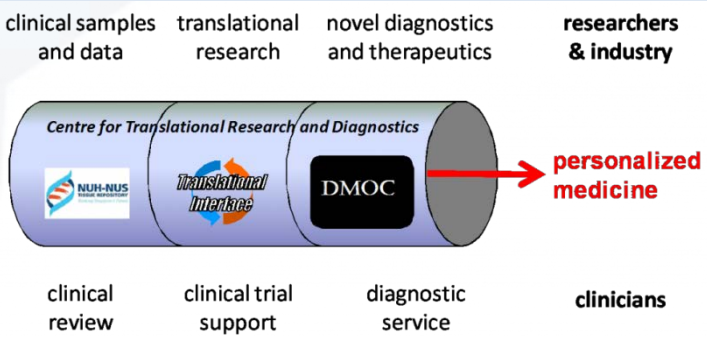
A joint venture between the Agency for Science, Technology And Research (A*STAR) and the National University of Singapore (NUS)

Genomics



A*STAR Genome Institute of Singapore

CENTRE FOR TRANSLATIONAL RESEARCH AND DIAGNOSTICS (CTRAD)



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Nurturing Talent

NUS National University of Singapore

NANYANG TECHNOLOGICAL UNIVERSITY

NMRC National Medical Research Council Singapore

Clinician Scientist Award

High school all the way to Post-doc

A*STAR Graduate Academy

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

MD-PhD Track

Industry Attachments

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Come Do Business

PHARMACEUTICALS & BIOTECHNOLOGY

EDB 'Home' Strategy

It is about extending Singapore's value proposition to businesses not just to help them improve their bottom line, but also to help them grow **their top line through establishing and deepening strategic activities** in Singapore to drive their business, innovation and talent objectives in Asia and globally. (Business, Innovation, Talent)

https://www.edb.gov.sg/content/edb/en/industries/industries/pharma-biotech.html

Clinical Trials Review and Approval

HSA Health Sciences Authority

Health Products Regulation Group, Clinical Trials Branch

Application for Clinical Trial Certificate (CTC) – 30 Working Days (Target Processing Timeline)

SingHealth RESEARCH

National Healthcare Group
Adding years of healthy life

DOMAIN SPECIFIC REVIEW BOARDS

Well established, experienced Institutional Review Boards with transparent processes

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HSA – Number of CTCs Issued

Phase	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
I	21	19	20	24	31	44	48	47	54	54	55	67	57	43	56
II	44	50	52	19	49	50	35	45	61	61	46	64	51	55	70
III	63	68	97	91	88	90	116	135	140	108	95	92	99	149	111
IV	29	28	26	26	32	17	18	26	31	39	38	42	43	50	43
Total	**157**	**165**	**195**	**160**	**200**	**201**	**217**	**253**	**286**	**262**	**234**	**265**	**250**	**297**	**280**

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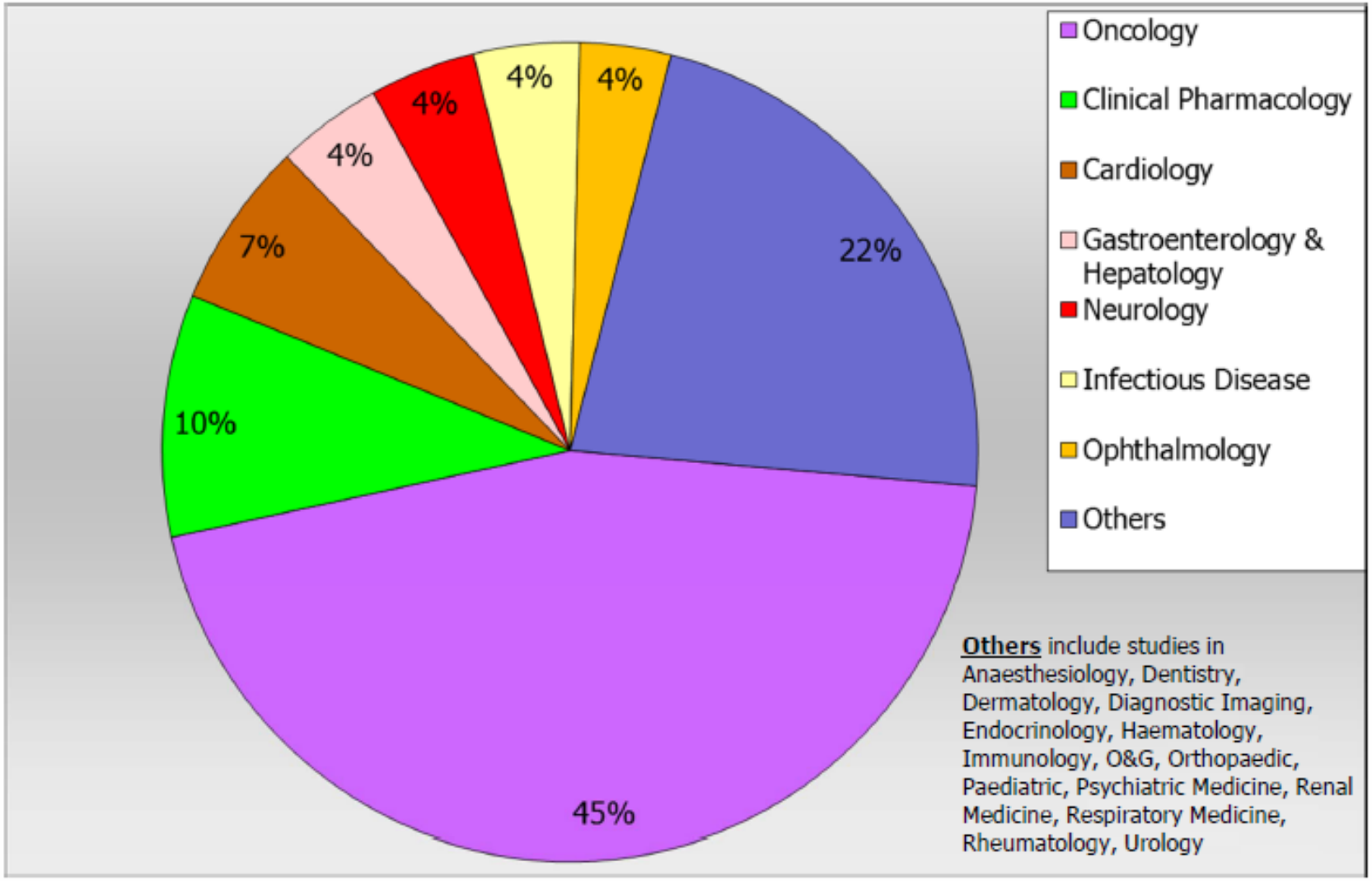
Clinical Trials by Therapeutic Area - 2014



Clinicaltrials.gov

Open Phase 1 Studies – 9th November 2015

- **Singapore - 245 studies**
  - Pop 5.47 million : 1 study per 22326
- **Hong Kong - 223 studies**
  - Pop 7.24 million : 1 study per 32466
- **Taiwan - 630 studies**
  - Pop 23 million : 1 study per 36507
- **China - 1544 studies**
  - Pop 1,401 million : 1 study per 907383
- **USA - 20367 studies**
  - Pop 321 million : 1 study per 15760

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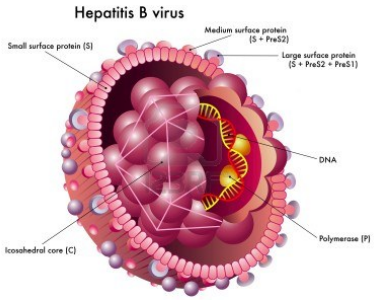
The Ecosystem is in Place

Case Studies

Hepatitis B Anti-Viral



Chronic Hepatitis B Infection Endemic in Asia

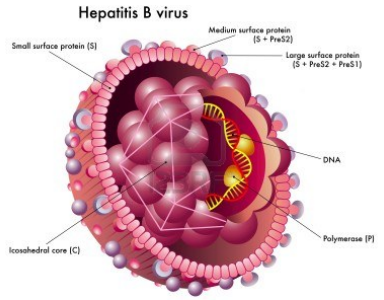
Huge Health Impact for the Individual and Health Systems

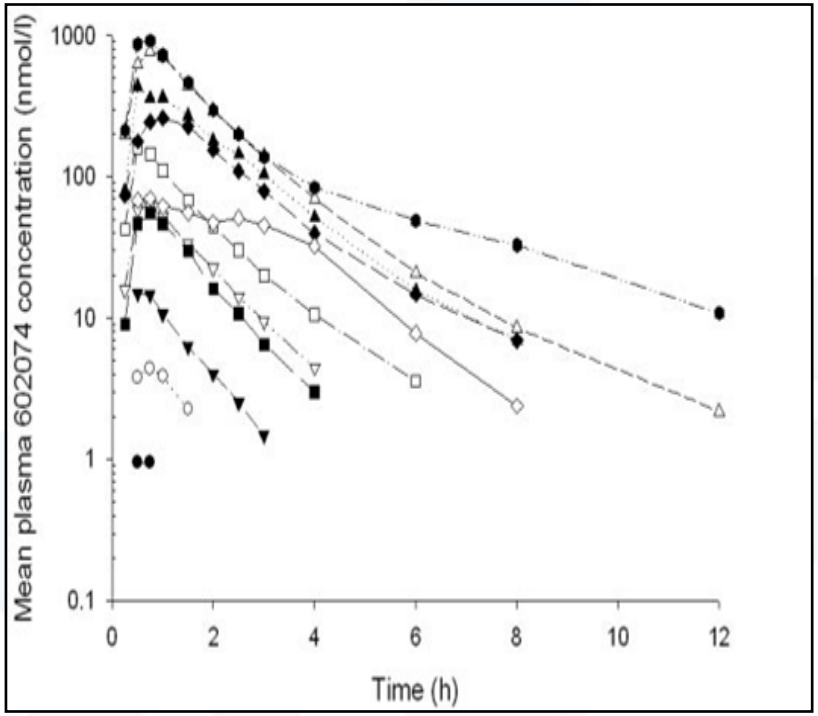
- Multiple Ascending dose PK and Safety study in HV (2 weeks)
- Multiple Ascending dose PK , PD and Safety study in Chronic Hep B infected patients (4 weeks)
- Screened 634 Chronic Hep B Patients, dosed 64

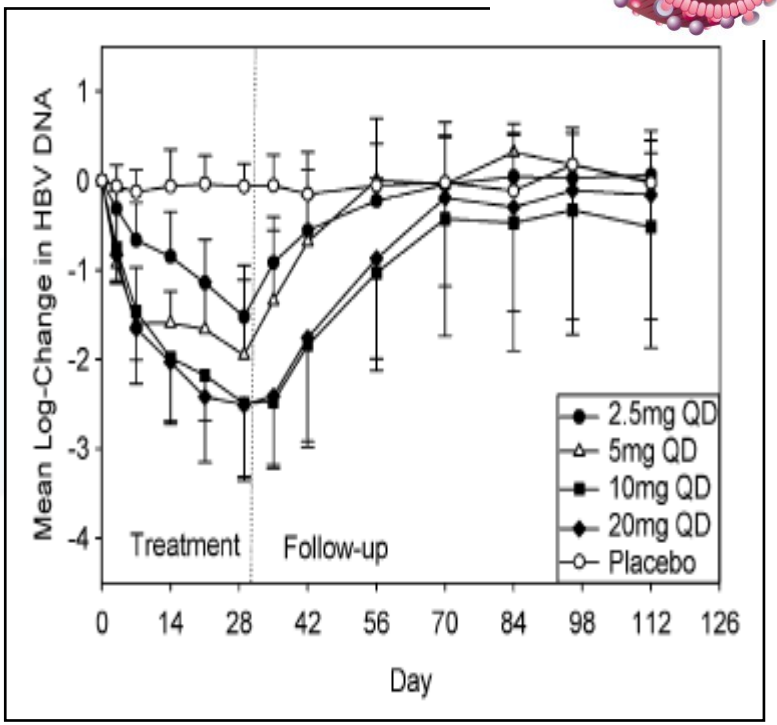
Safety and efficacy of alamifovir in patients with chronic hepatitis B virus infection.
Soon DK, Lowe SL, Teng CH, Yeo KP, McGill J, Wise SD. *J Hepatol*. 2004 Nov;41(5):852-8.

Clinical pharmacokinetics of alamifovir and its metabolites.
Chan C, Abu-Raddad E, Golor G, Watanabe H, Sasaki A, Yeo KP, Soon D, Sinha VP, Flanagan SD, He MM, Wise SD. *Antimicrob Agents Chemother*. 2005 May;49(5):1813-22.

Hepatitis B Anti-Viral







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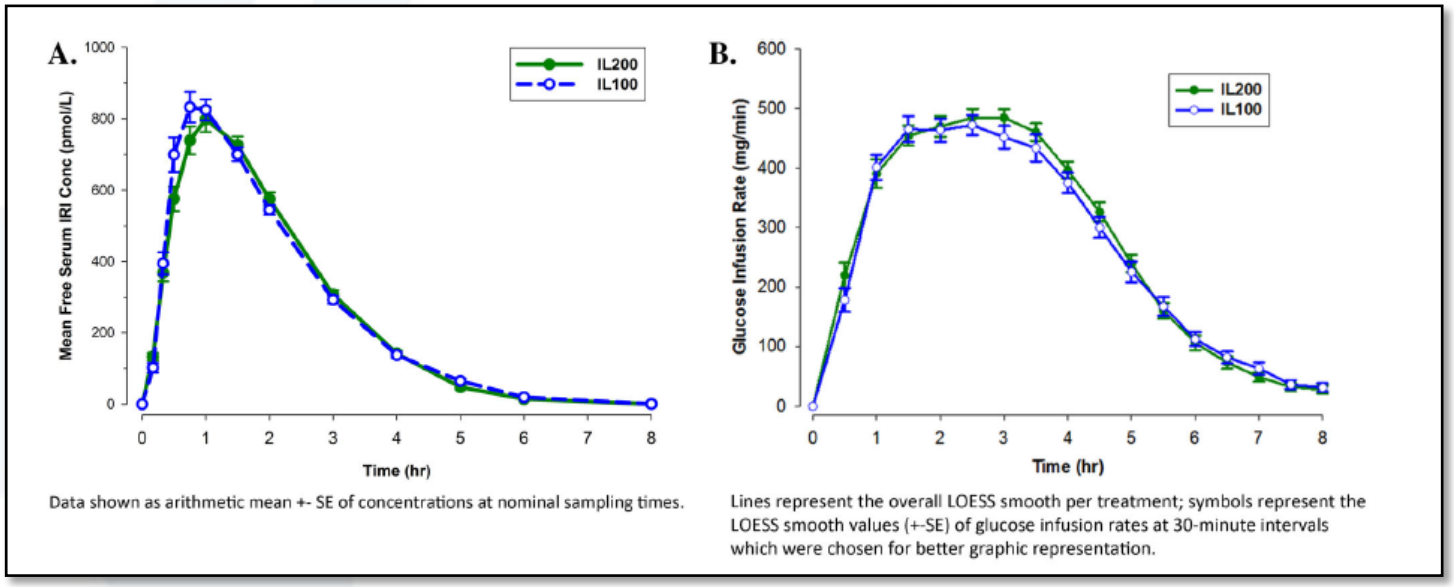
Pivotal Insulin Studies

Journal: *Clinical Pharmacology in Drug Development (Electronic) Oct 2015*
"Bioequivalence and Comparative Pharmacodynamics of Insulin Lispro 200 Units/ml Relative to Insulin Lispro (Humalog®) 100 Units/ml" Amparo de la Pena , Mary Seger , Danny Soon, Adam J. Scott, Shobha R. Reddy, Michael A. Dobbins, Patricia Brown-Augsburger, and Helle Linnebjerg



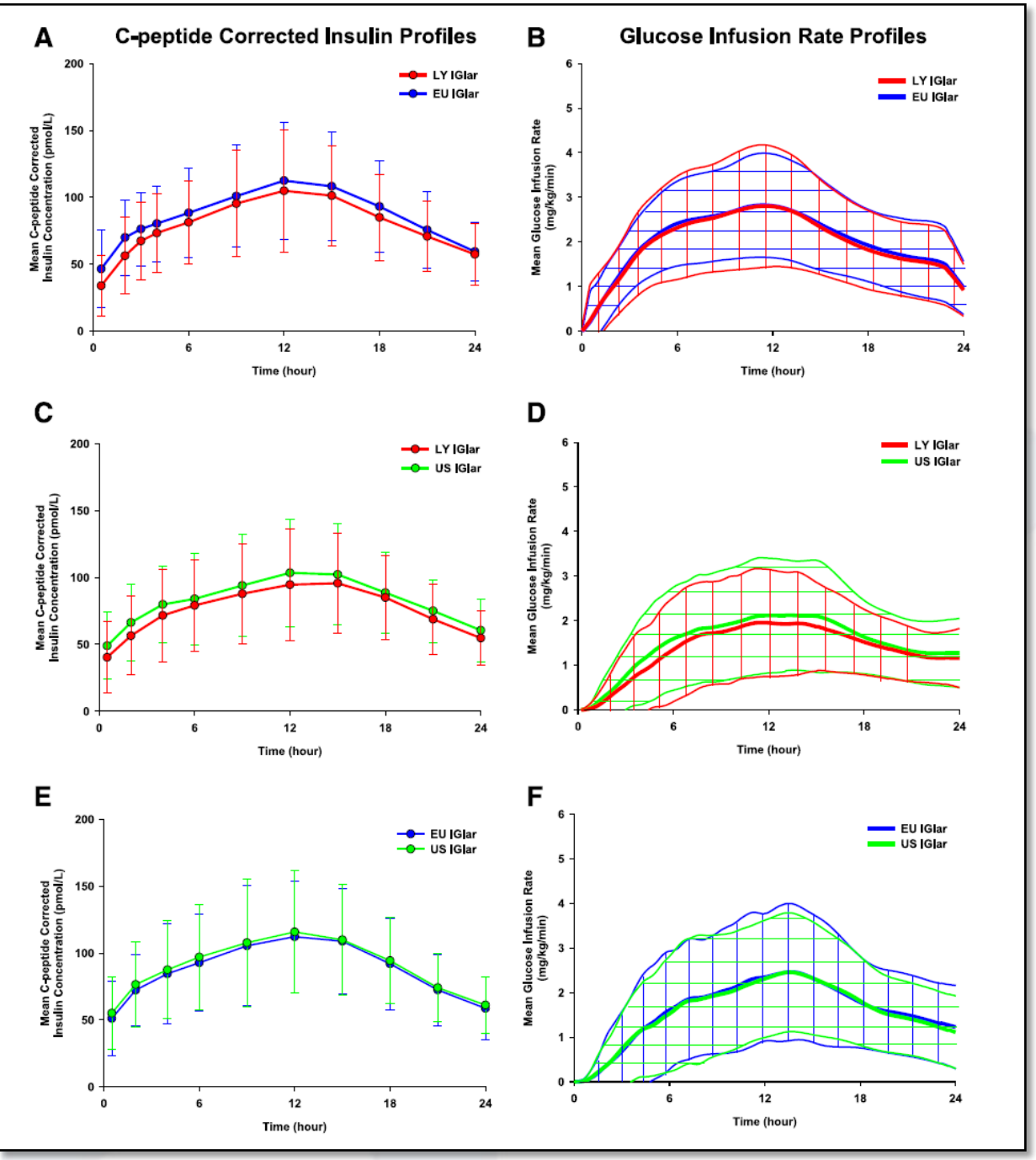
Data shown as arithmetic mean +- SE of concentrations at nominal sampling times.

Lines represent the overall LOESS smooth per treatment; symbols represent the LOESS smooth values (+-SE) of glucose infusion rates at 30-minute intervals which were chosen for better graphic representation.

INDIANAPOLIS, May 27, 2015 /PRNewswire/ -- The U.S. Food and Drug Administration (FDA) has approved Humalog® 200 units/mL KwikPen® (insulin lispro 200 units/mL; U-200), a pre-filled pen containing a concentrated formulation of Lilly's rapid-acting insulin Humalog® (insulin lispro 100 units/mL) Humalog U-200 KwikPen marks the first FDA approval of a concentrated mealtime insulin analog.

Insulin U200 Registration in the EU and US

Pivotal Insulin Studies



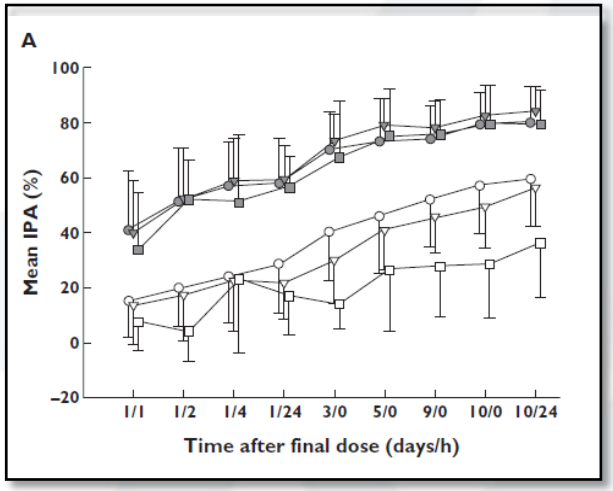
Comparison of the Pharmacokinetics and Pharmacodynamics of LY2963016 Insulin Glargine and European Union- and U.S.-Approved Versions of Lantus Insulin Glargine in Healthy Subjects: Three Randomized Euglycemic Clamp Studies.

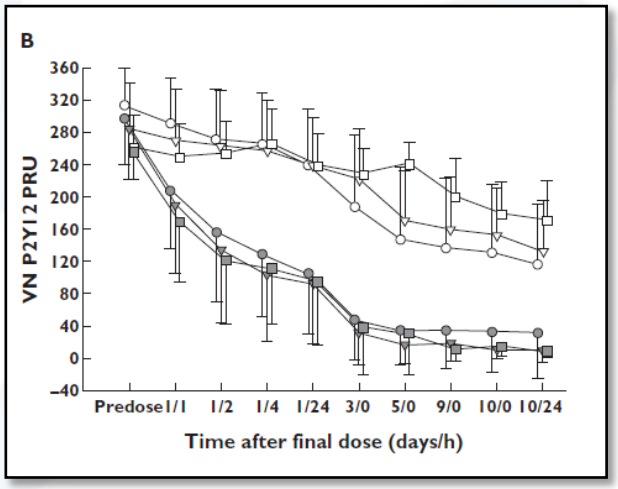
Linnebjerg H, Lam EC, Seger ME, Coutant D, Chua L, Chong CL, Ferreira MM, Soon D, Zhang X. Diabetes Care. 2015 Aug 25. [Epub ahead of print]

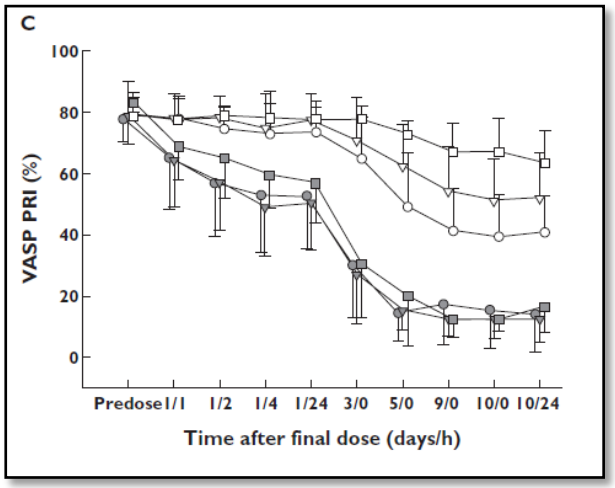
INDIANAPOLIS, Aug. 18, 2014 /PRNewswire/ -- The U.S. Food and Drug Administration (FDA) today granted tentative approval for Basaglar™

Interethnic/Phenotypic Comparisons

Pharmacokinetics and pharmacodynamics following maintenance doses of prasugrel and clopidogrel in Chinese carriers of CYP2C19 variants.
Kelly RP, Close SL, Farid NA, Winters KJ, Shen L, Natanegara F, Jakubowski JA, Ho M, Walker JR, Small DS. Br J Clin Pharmacol. 2012 Jan;73(1):93-105.







Prasugrel Label: In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel**, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics** of prasugrel's active metabolite or **its inhibition of platelet aggregation.**

Interethnic/Phenotypic Comparisons

Comparison between 8 Asian Indians and 8 Chinese in Singapore

Single Dose of Warfarin 25mg, as part of DDI study

Genotyped for CYP2C9 (Warfarin PK), and VKORC1 (Warfarin PD)

Higher S-Warfarin Exposures in Indians due to CYP2C9 Intermediate Metaboliser status

BUT

Lower INRs due to H7/H7 VKORC1 Haplotype (Warfarin Resistant)

Ethnic differences in the population pharmacokinetics and pharmacodynamics of warfarin. Yuen E, Gueorguieva I, Wise S, Soon D, Aarons L. J Pharmacokinet Pharmacodyn. 2010 Feb;37(1):3-24.

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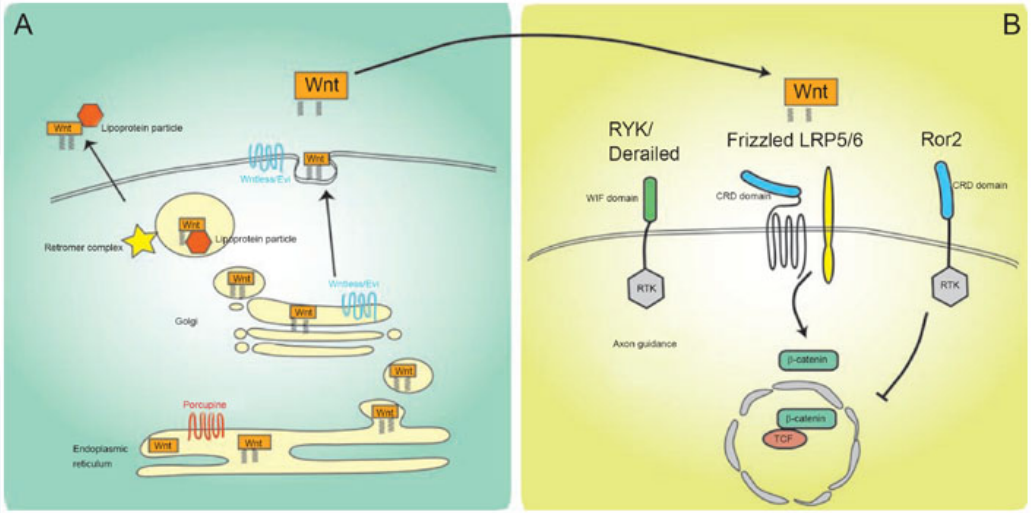
Wnt-Porcupine Inhibitor

Experimental Therapeutics Centre
A*STAR

"A made-in-Singapore cancer drug has advanced into clinical trials" – June 2015



DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

National Cancer Centre Singapore
SingHealth

A*STAR D3

Experimental Therapeutics Centre

Wnt-Porcupine Inhibitor

- “ETC-159, was developed in a collaboration between A*STAR and Duke-NUS, and is expected to target a range of cancers, including colorectal, ovarian and pancreatic cancers.

- This is the first publicly-funded drug candidate discovered and developed in Singapore to advance into first-in-human trials

- ❖ Discovery Biology
- ❖ Target Validation
- ❖ Medicinal Chemistry
- ❖ Pre-clinical Development
- ❖ Phase 1 FIH Study

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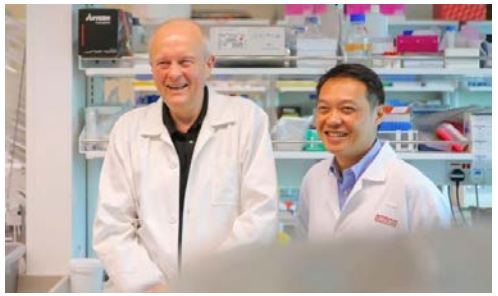
Dengue Monoclonal Antibody

SMART
Singapore-MIT Alliance for Research and Technology



"Engineered Antibody Neutralizes All Four Dengue Serotypes"

http://www.asianscientist.com/2015/07/topnews/visterra-dengue-therapeutic-antibody-serotypes/

DUKE NUS GRADUATE MEDICAL

A*STAR D3
CREATING GROWTH. ENHANCING LIVES.

Visterra

NUS National University of Singapore

NANYANG TECHNOLOGICAL UNIVERSITY

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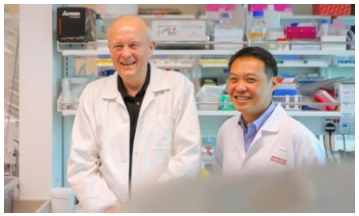
Dengue Monoclonal Antibody

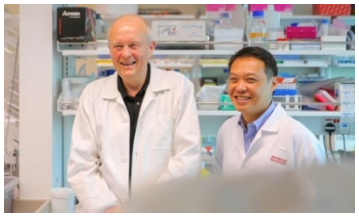


Collaborative Research between

- Singapore-MIT Alliance for Research and Technology (SMART),
- Duke-NUS Graduate School of Medicine (Duke-NUS),
- National University of Singapore (NUS)
- Nanyang Technological University (NTU)
- Visterra Inc.
- A*STAR/D3

"The antibody is now being developed by Visterra, in partnership with D3 of A*STAR for clinical trials next year (2016)."

Dengue Monoclonal Antibody



- Biology
- In-house animal infection model
- mAb design
- Cell lines, Manufacturing and scale up
- Pre-clinical development
- *Clinical development

Leveraging on the ‘brain trust’ in Singapore

Integrated Biomedical Research

Niche and Specialty CROs and Technologies

Clinical Imaging Research Centre Singapore

InVivos — Bringing Life to Your Research

AMRI

Prestige Bio Research PBR

Early-phase Clinical Trial Units

NUHS National University Health System

SingHealth

Changi General Hospital SingHealth

Big 5 CROs

ICON — A Symbol of Excellence

COVANCE

PPD

PAREXEL

QUINTILES

Regulatory and Ethical Review

HSA Health Sciences Authority

SingHealth Research

National Healthcare Group — Domain Specific Review Boards

Drug Development Vehicles

ASLAN Pharmaceuticals

A*STAR D3

Hospitals, Specialty Institutes

One of world's Top 10 Healthcare services

Singapore General Hospital SingHealth

Tan Tock Seng Hospital

NUH National University Hospital

National Cancer Centre Singapore SingHealth

Fortis Colorectal Hospital

National Skin Centre

Singapore Eye Research Institute

Eastern Health Alliance

Academic Medical Centres

Robust pipeline of clinician-scientist thought leaders

SingHealth Duke-NUS Graduate Medical School

NUHS National University Health System

NUH National University Hospital

NUS National University of Singapore

Tan Tock Seng Hospital

Lee Kong Chian School of Medicine

Redefining Medicine, Transforming Healthcare

Nanyang Technological University

Summary

- Advanced Healthcare System
- Investment in Biomedical Research
- Pro – Industry Outlook
- Effective supporting functions

Strong Ecosystem for Translational and Early Phase Clinical Research

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THANK
YOU