Drug Discovery, Development and Commercialization, Winter 2013

Ronald J. Christopher, Ph.D., D.A.B.T., FCP

"Compound Selection & Preclinical Studies"

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Preclinical Research & Development Overview

- Pharmaceutical R&D Paradigm
- Compound Selection
- Preclinical R&D Activities
  - Pharmacology
  - Drug Metabolism & Pharmacokinetics
  - Drug Safety
- Case Example & Clinical Translation

Discovery To Market – The Economics

Time:

Discovery → IND:	1-5 years
IND → NDA/BLA:	~ 6 years
Review/Approval Time:	1.1 years avg

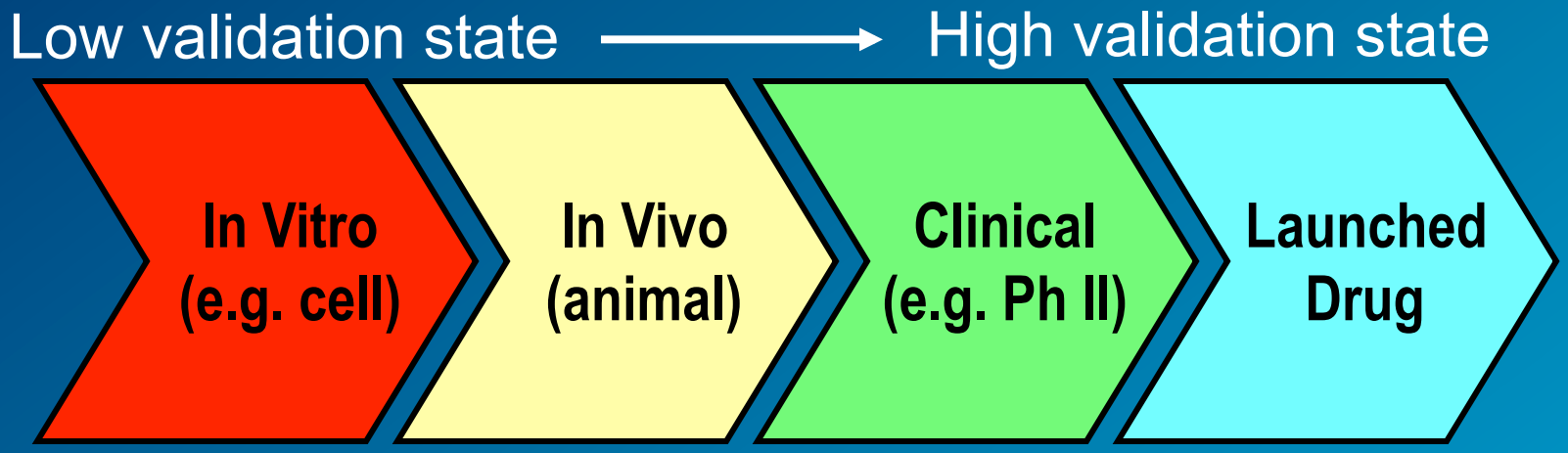
Expense:

The cost of developing a new drug is higher than ever — about $1.3 billion

Success Rate of Drug Development

- Candidates for a new drug to treat a disease might include from 5,000 to 10,000 chemical compounds.
- On average about 250 of these show promise for further development
- About 10 of these will progress to human clinical trials
- Research to Market Success rate: ~1 in 1,000 compounds

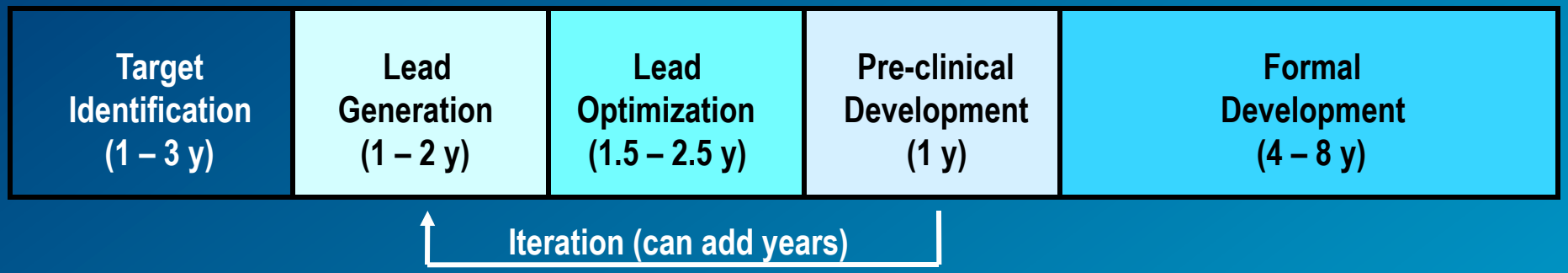
R&D Focus on Validation State of Targets



>70% of all marketed drugs result from R & D efforts on previously clinically validated targets

Compressing the Drug Discovery Process?

Average Industry R& D Timeline: >12 Years



Desired R& D Timeline: < 7 years

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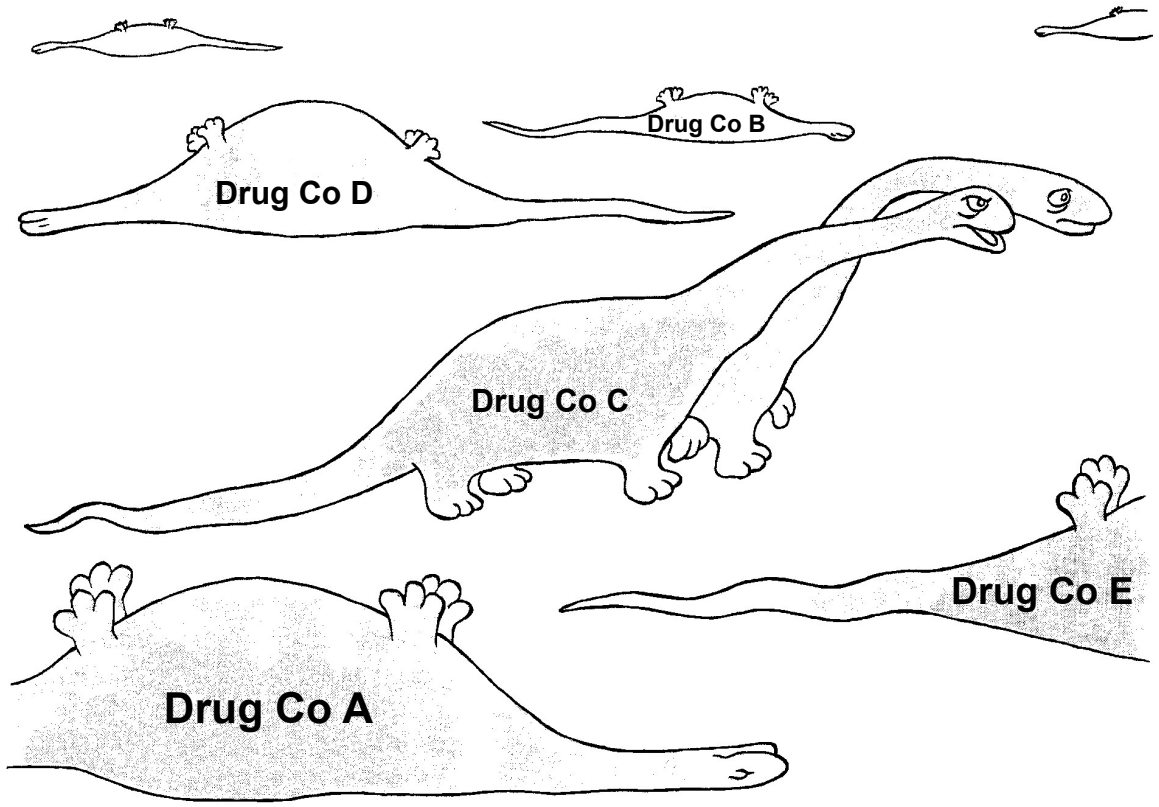
Taking Shortcuts

- We **can't afford** to collect *extra* data in the R&D Process
- Therefore, optimal efficiency in R&D is critical

CORPORATE FINANCE

"You wanna spend WHAT?!?"

How Do We Improve?



"Frankly, I don't like the way things are going."

http://www.fda.gov/oc/initiatives/criticalpath/stanski/stanski.html

The new paradigm for drug R&D

- Integration of skills
- Joint ownership/responsibility

Discovery **Preclinical** **Clinical**

Input from Business Development, Regulatory Affairs, Project Management, Legal

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Compound Selection

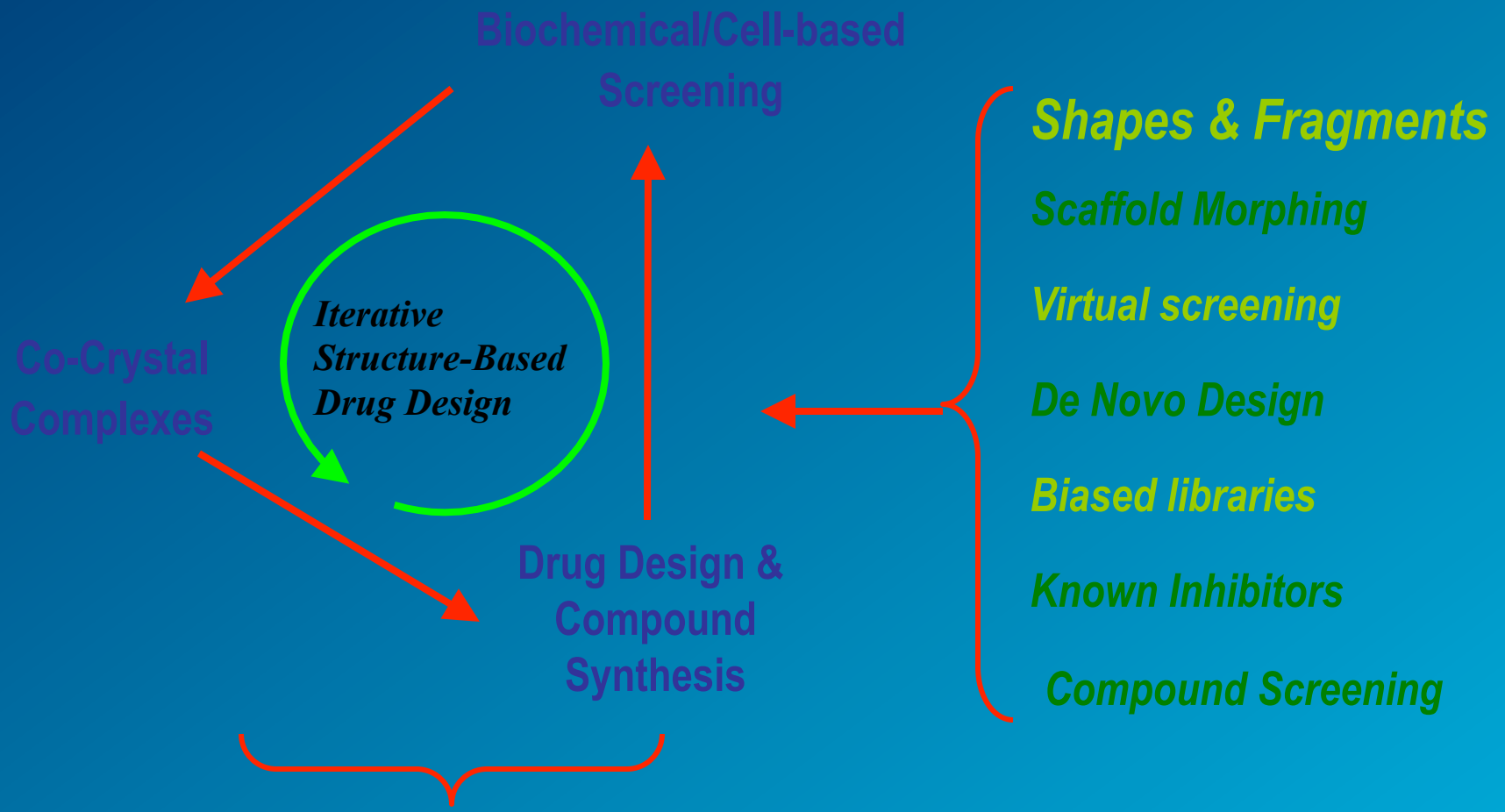
Target Choice

- A good target has distinctly different meaning to biology and chemistry personnel
- In a biology sense, a good target is a biological pathway that can be intercepted in some way to give a useful therapeutic outcome
- In a chemistry sense, a good target is a biological pathway that can be intercepted in a useful sense by an orally active small organic molecule
- Interplay of the disciplines leads to success

Typical Compound Criteria in Research

- Focus on First-in-Class or Best-in-Class
- Structurally unique molecule
- Solid Pharmacology
  - Potency that meets or exceeds Gold standard
  - Target selectivity >1,000 fold selective vs. closely related target
  - Efficacy in relevant animal models (durability of response important)
- Excellent Drug Metabolism & Pharmacokinetic Properties
  - No DDI liabilities
  - Suitable for Q.D dosing (if oral)
  - Limited metabolism, etc.
- Robust Efficacy in rodent autoimmune disease models
- Excellent Safety profile (in vitro, in vivo)

Lead Generation Strategy



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Research Testing Cascade

First tier screens

- Receptor Binding [EC_{50} < 10 nM]
- Solubility [0.1 - 0.2 mg/mL aq pH7]
- HLM / MLM / RLM $T_{1/2}$ stability > 60'
- hERG binding [^{3}H]-Astemizole > 10 μM
- HepG2 cytotoxicity panel IC_{50} > 100 μM
- Human 5 major P450s [microsomal]
- Protein binding [human / rodent] < 95 %
- Mini AMES [+/- S9]

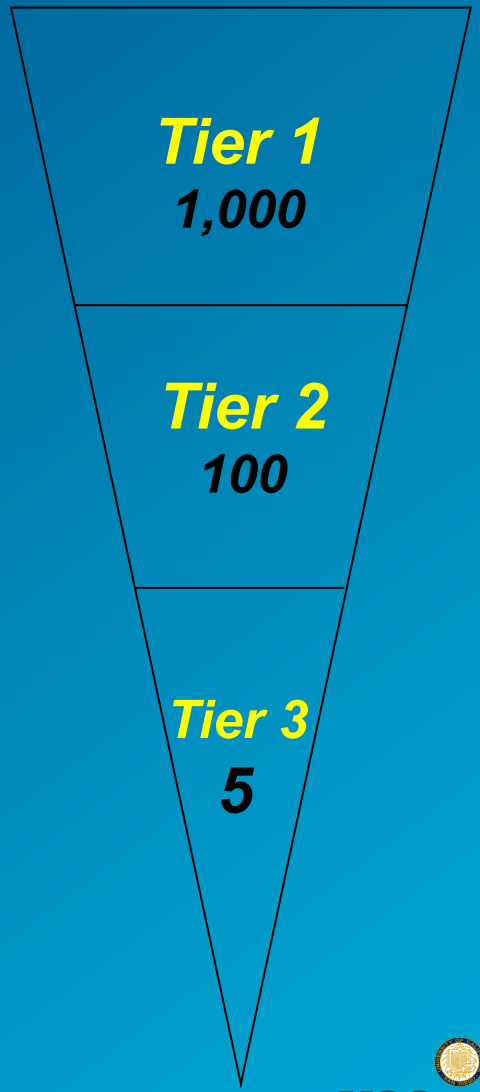
Second tier studies

- Oral efficacy & Dose Response [ED_{50} ~ 1 mpk]
- Mouse PK / PD
- Single dose iv/po, SD rat and mouse [PK/PD)
- Cardiotox.: hERG
- CEREP panel
- Ames mutagenicity [+/- metabolic activation]

Third tier studies

- Primary disease model : Mouse, Rat efficacy
- *in vitro* metabolism, metabolite ID
- Dose escalation PK
- Single dose IV/PO dog, monkey PK/PD
- Dog CV / rodent telemetry
- Pharm. Sci. [solid state testing, preformulation]

Metrics



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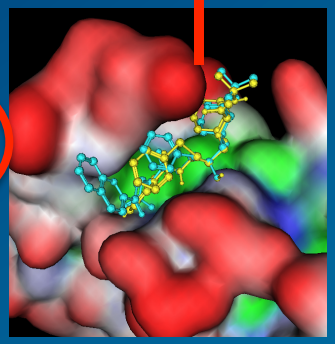
Typical Research Assay Flow Scheme

Chemistry → Enzyme/Ligand Assays

Target



$IC_{50} \leq 100$ nM

Ligand Selectivity
(off-targets or closely related targets)

Selectivity > 1000-fold

- Rat/Dog Plasma DPP4 Inhibition
- Human/Rat/Dog microsome stability
- CYP450 inhibition
- Solubility
- Protein binding

- Rat PK/PD (iv and po)
  - Ligand inhibition (PD)
  - Plasma conc. timecourse

Lead Series Declaration

- Safety pharmacology
  - e.g., Cerep
- initial rodent toxicology
- Non-rodent PK
- hERG Channel
- Genetic toxicity

Candidate Selection

Development (IND enabling studies)

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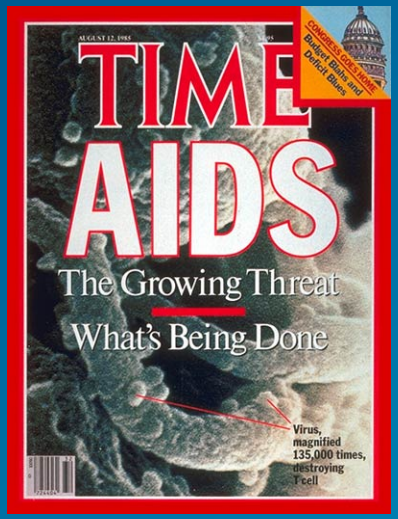
Case Example

Structural Biology in Drug Discovery

An increasing role in understanding disease and in the design of new medicines

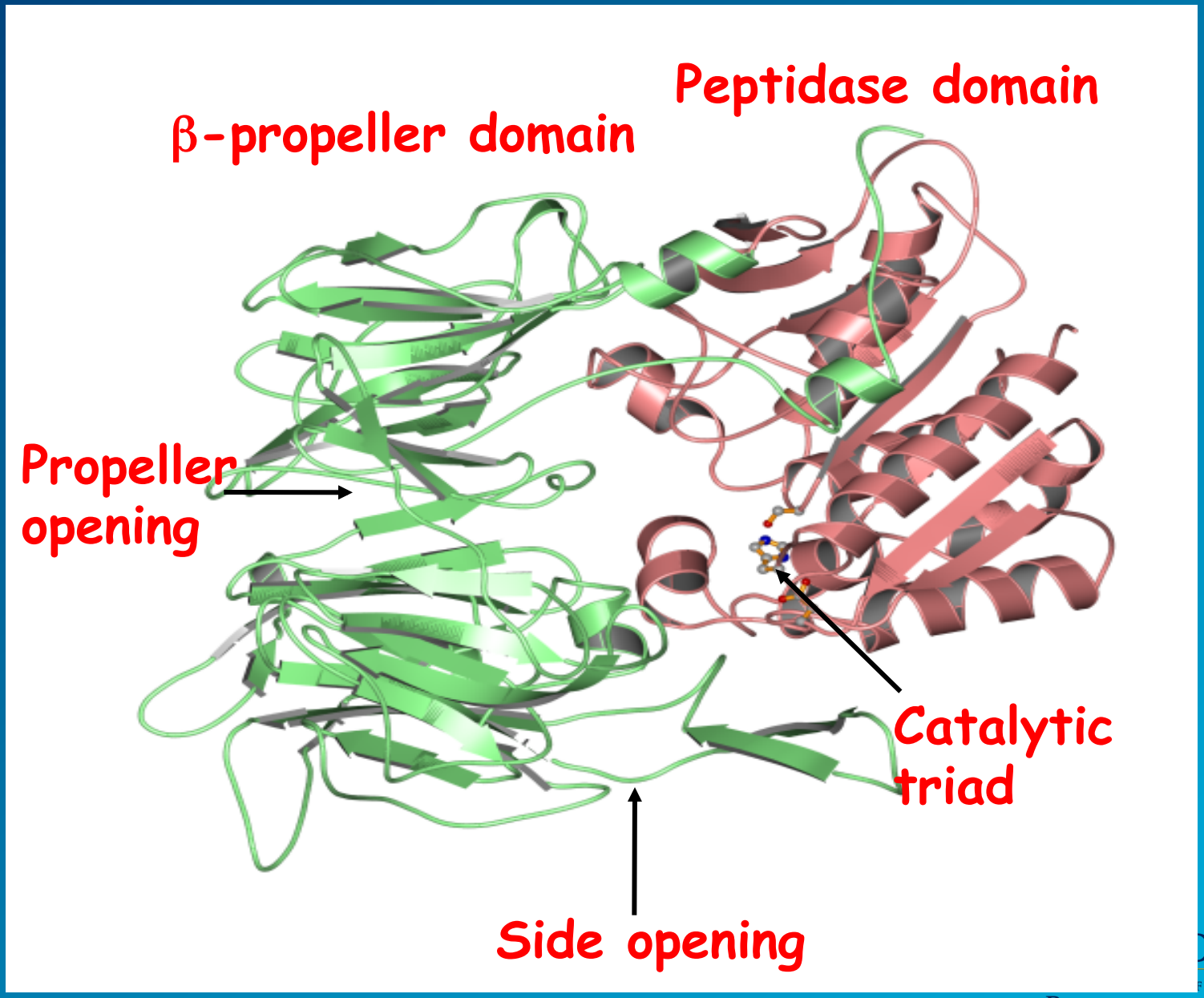


Viracept
Agenerase

Gleevec

Actos
Nesina

Atomic Structure of DPP-4 Protein

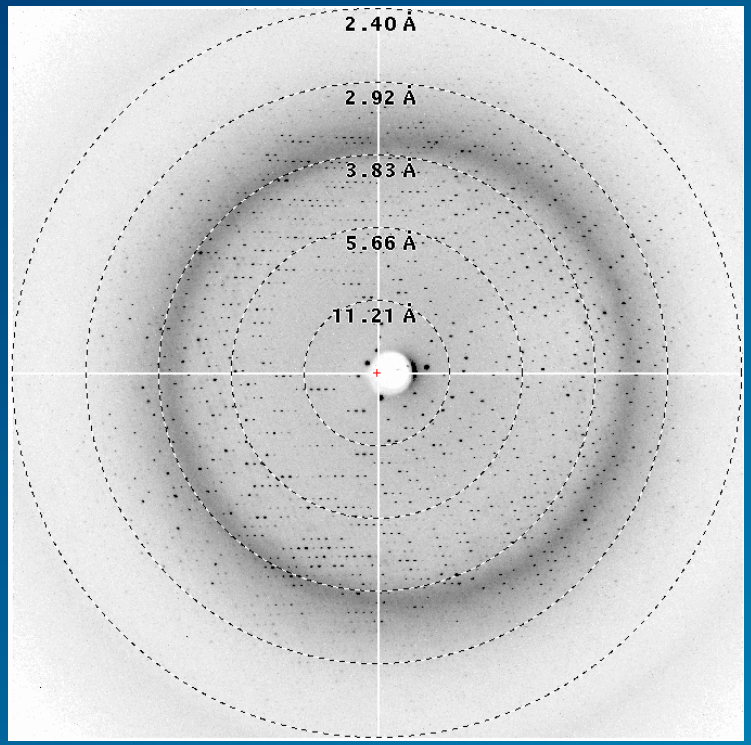


Structural Biology adopts the use of X-rays in the design of new medicines…

But how can X-rays be used to take a picture of a protein target involved in a human disease and then design a drug for that target?

X-Ray Crystallography

Diffraction Pattern



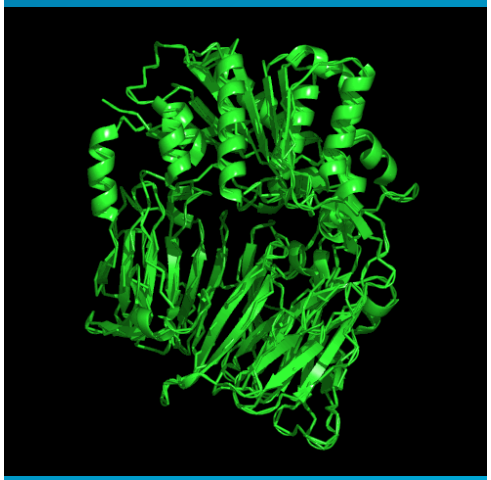
Crystal

Source

X-Rays

X-Ray Wavelength: 1Å
C – C bond length: 1.5Å

+ Phases



Structure

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DPP-4 Inhibitor Program Critical Success Factors

- Absolute Criteria:
  - Highly selective and very potent
  - No CYP450 interactions
  - Once-daily dosing
  - Orally active
  - Superior Efficacy and safety profiles
- Relative Criteria:
  - Equivalence or superiority to best known competitor DPP-4 inhibitors on all significant parameters
  - Key comparator compounds: Novartis (Galvus) and Merck (Januvia)

Overall Goal: A Best-in-Class DPP-4 Inhibitor

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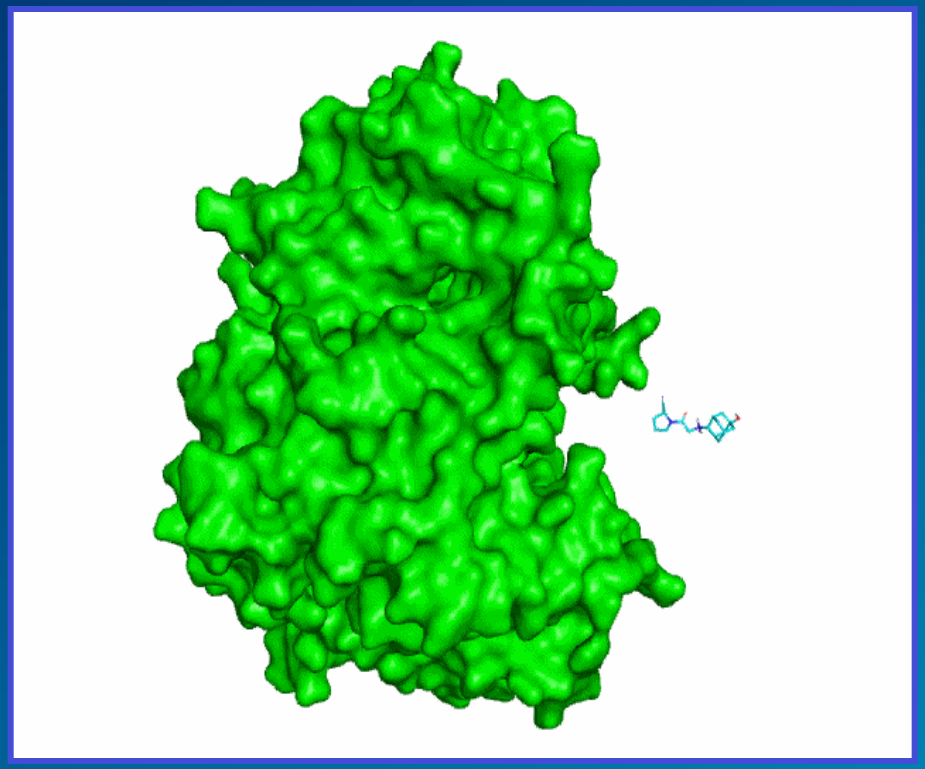
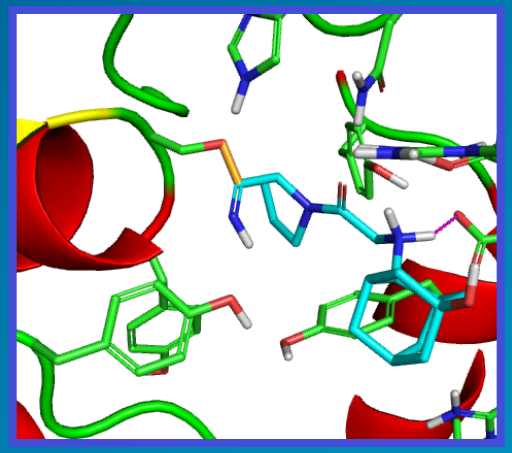
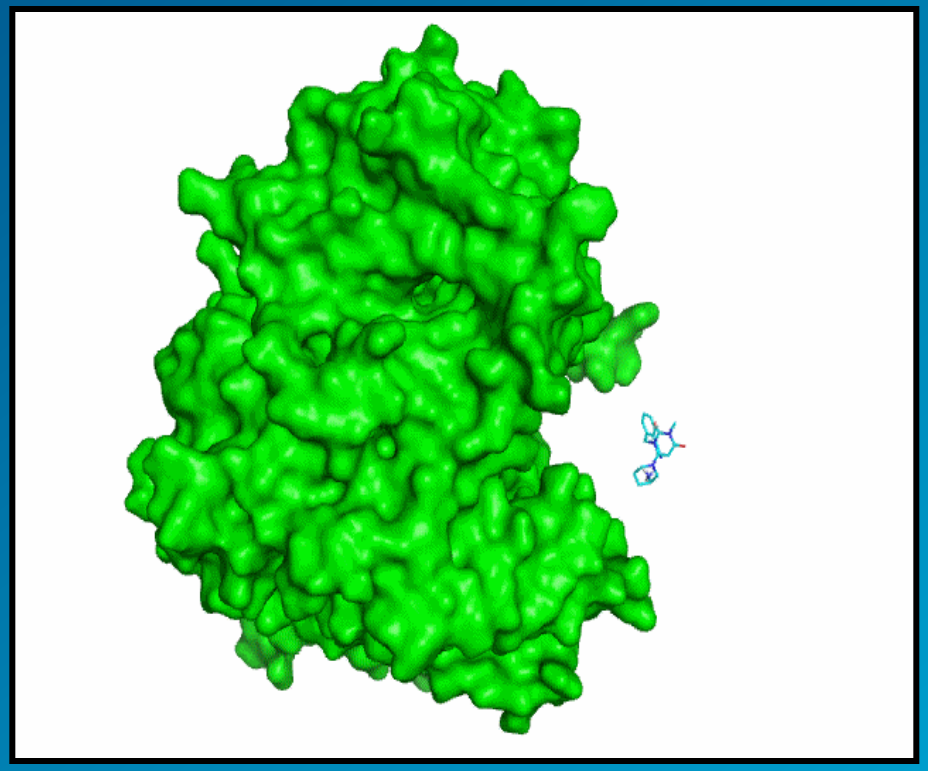
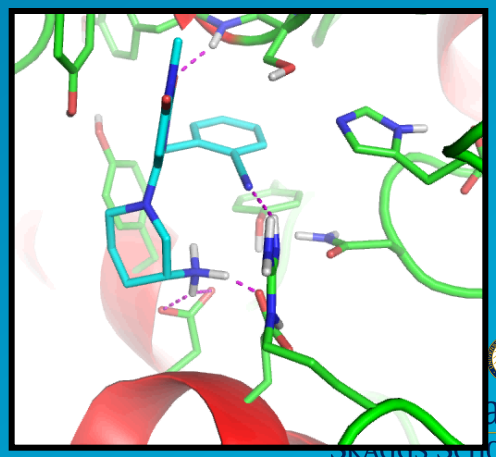
Vildagliptin



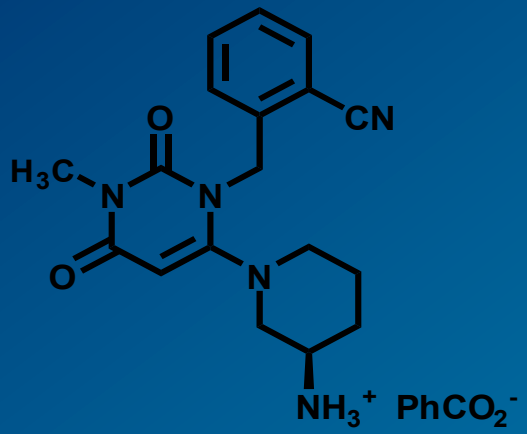


Alogliptin



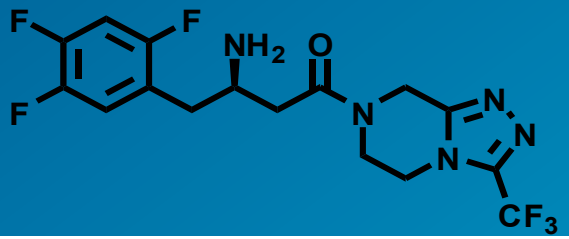


Structures of DPP-4 Inhibitors



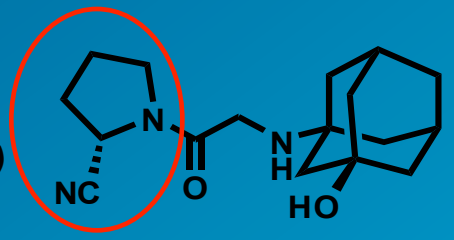
Alogliptin

non-covalent



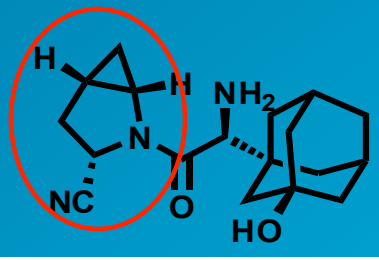
Januvia (Sitagliptin)

covalent (cyanopyrrolidine)



Galvus (Vildagliptin)

covalent (cyanopyrrolidine)



Saxagliptin

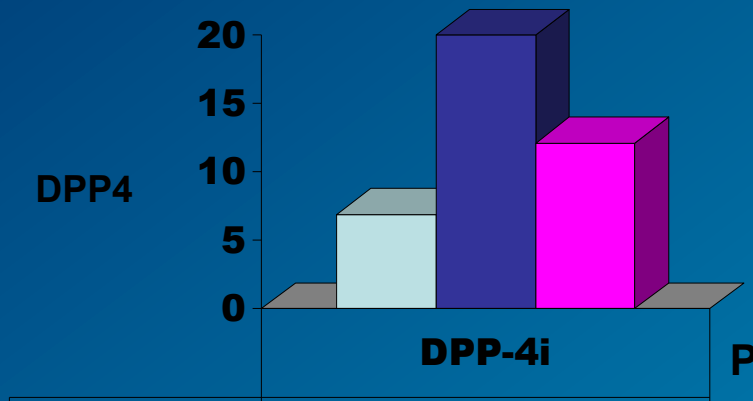
DPP-4 Related Enzymes

- Inhibitors thought to be specific for DPP-4 may inhibit other enzymes in the "DPP-4 activity and/or structural homologue" (DASH) family

- Include:
  - FAPα/Seprase
  - DPP-2
  - DPP-8
  - DPP-9
  - PREP
  - Tryptase

- Biological role of related proteases:
  - T-cell apoptosis
  - Attenuating T-cell activation
  - Inactivation of regulatory neuropeptides
  - Pathogenesis of cancer (promoting growth & metastasis)

Alogliptin: DPP-4 Potency & Selectivity Comparisons



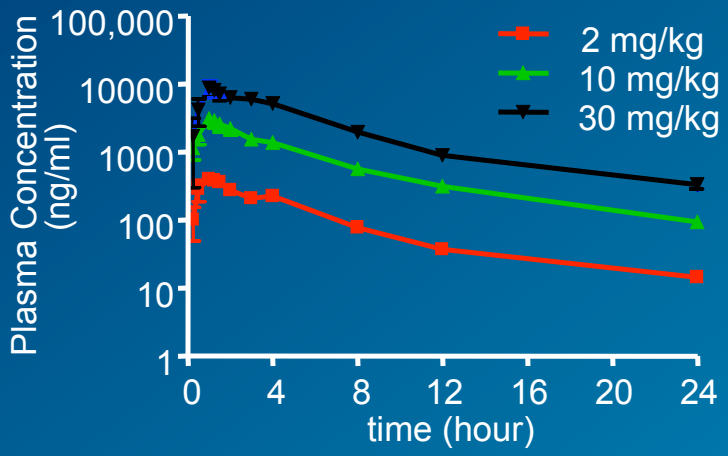
	DPP-4i	Potency
Alogliptin	6.9	++++
Galvus	23.8	+
Januvia	12.1	++

- Alogliptin is a potent DPP-4 inhibitor with high selectivity against related serine proteases
- DPP-8 and DPP-9 activity appear to correlate with toxicities in animals and may be a key liability

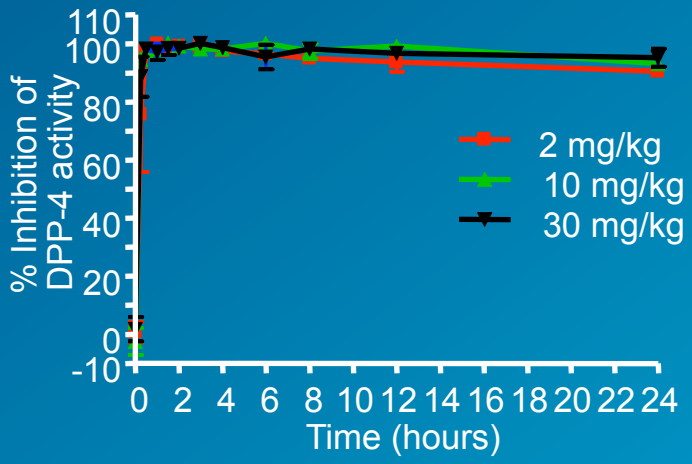
IC_{50} (nM) for each enzyme

Compound	DPP-2	DPP-8	DPP-9	FAP	PREP	Tryptase
Alogliptin	> 100,000	> 100,000	> 100,000	> 100,000	> 100,000	> 400,000
Galvus (Vildagliptin)	> 100,000	1,400	81.5	73,000	> 50,000	> 200,000
Januvia (Sitagliptin)	> 50,000	19,000	62,000	> 100,000	> 100,000	> 400,000

Plasma Concentrations and DPP-4 Inhibition in Monkeys on Alogliptin (PO Dosing)



- Dose linear pharmacokinetics
- $T_{1/2}$ (PO) = 6 hours
- %F = >80%



- Inhibition initiated at 0.25 hours post dose
- Maximum DPP-4 inhibition at 2 to 3 hours post dose (90% to 91%)

Pharmacology

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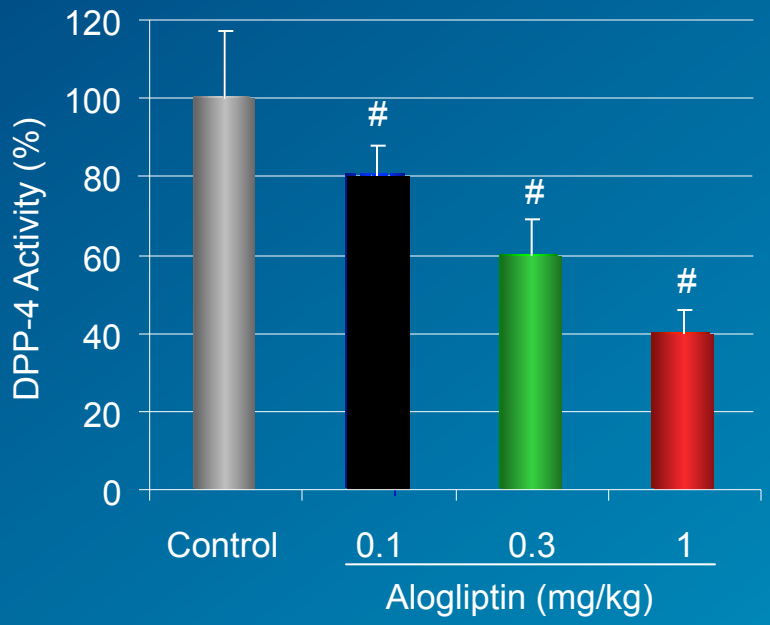
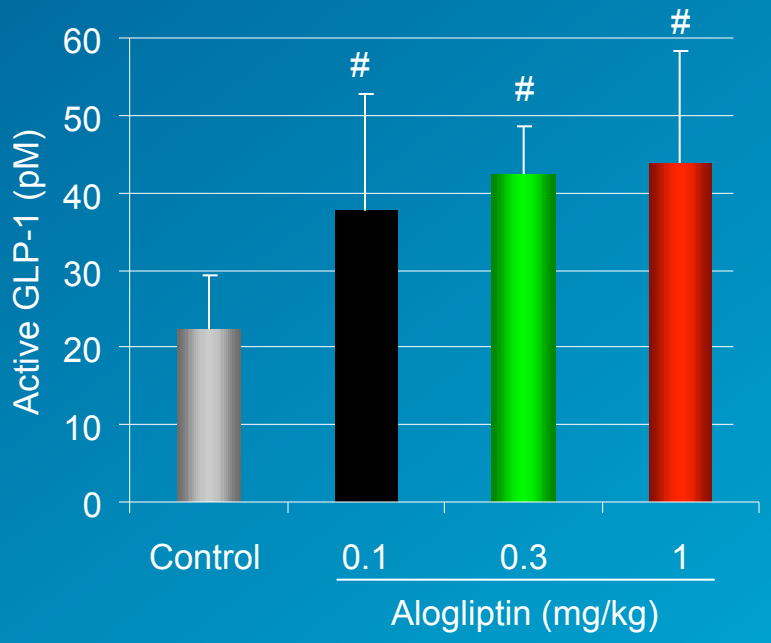
Alogliptin Reduces DPP-4 Activity and Increases Active GLP-1 Levels

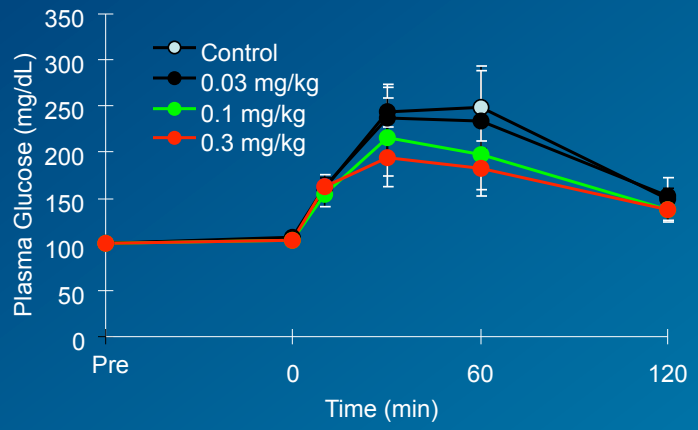
Non-Obese/Diabetic N-STZ-1.5 Rats

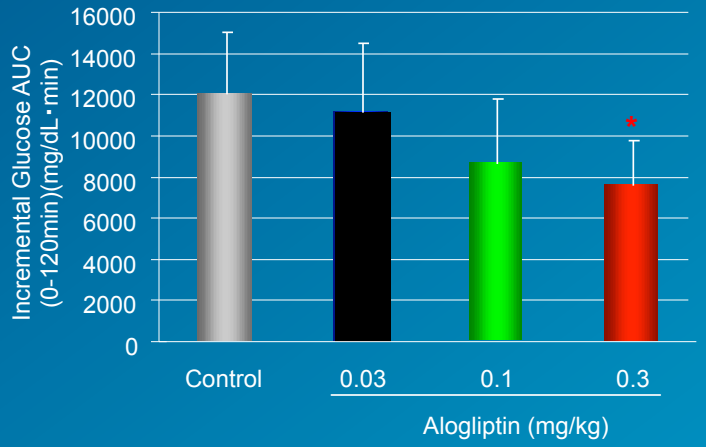


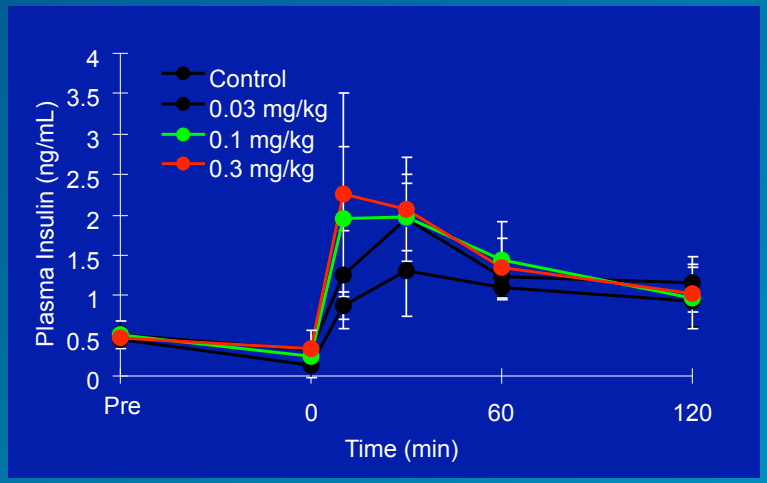


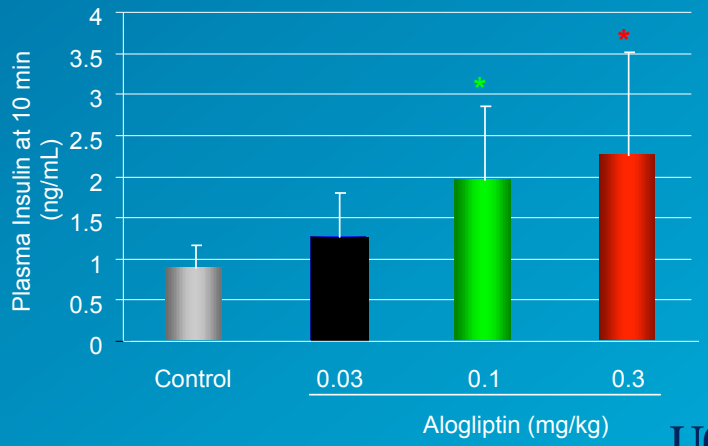
Alogliptin orally administered 1.5 h before meal load.
Mean and SD, N=8, #$P \leq 0.025$

Alogliptin Lowers Plasma Glucose and Increases Plasma Insulin (OGTT in N-STZ-1.5 Rats)









Mean and SD, N=6, ∗$P \leq 0.025$

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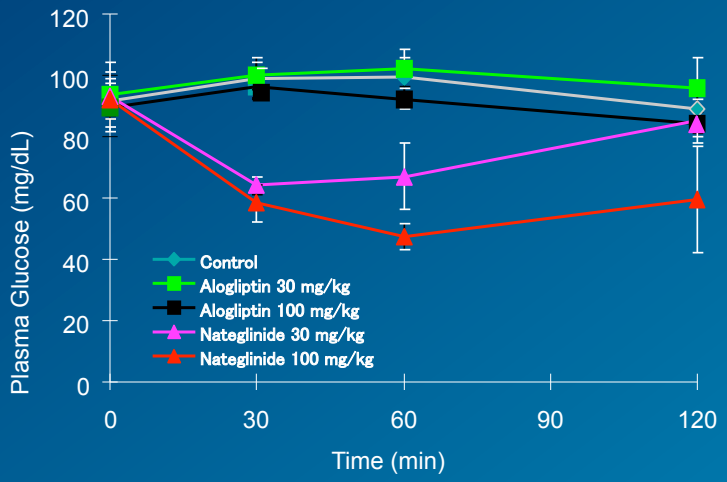
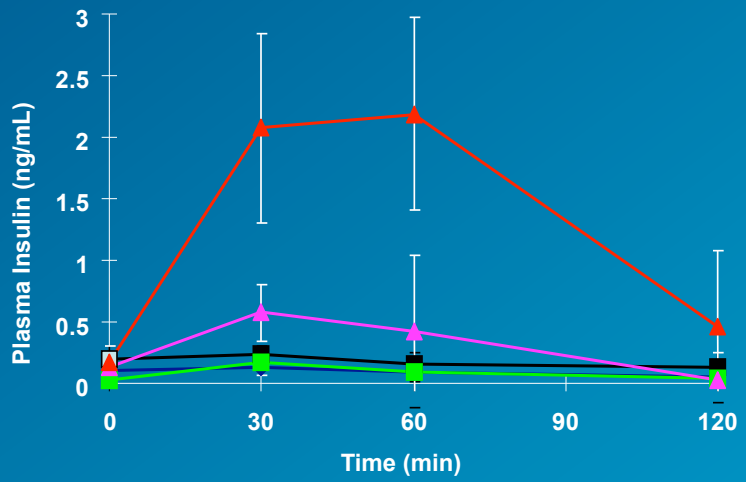
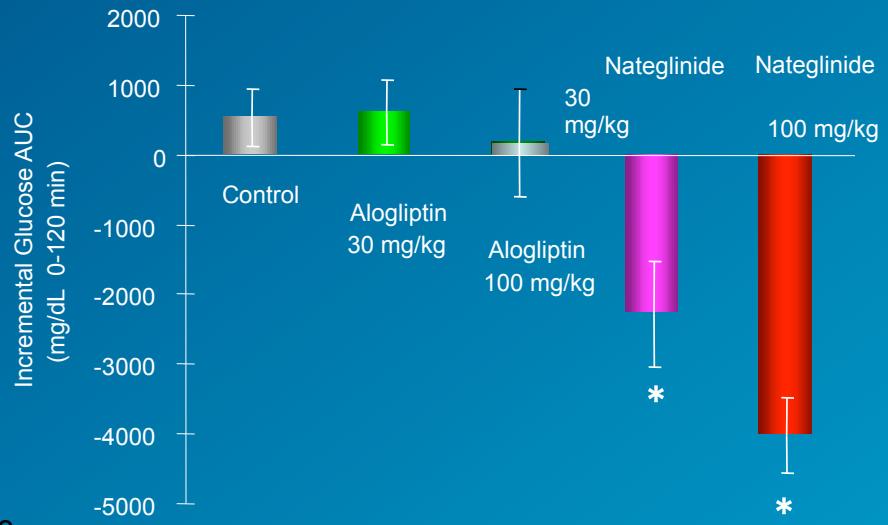
Effects on Fasting Plasma Glucose in Normal SD Rats







Fasting Sprague-Dawley rats (7 wks old, male) were orally administered alogliptin or nateglinide at 0 min.
Mean ± SD, N=6. *$P \leq 0.025$

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Alogliptin *In Vivo* Pharmacology (multiple doses)

Alogliptin in *db/db* mice

***db/db* (N=8) and *db/+* (n=5) mice (8 week-old)**

Dietary admixture: CE-2 powder diet containing 0.01%, 0.03%, 0.1% of Alogliptin for 2 days

0.01% ≅ 14 mg/kg
0.03% ≅ 42 mg/kg
0.1% ≅ 140 mg/kg

Plasma DPP-IV activity and GLP-1 levels

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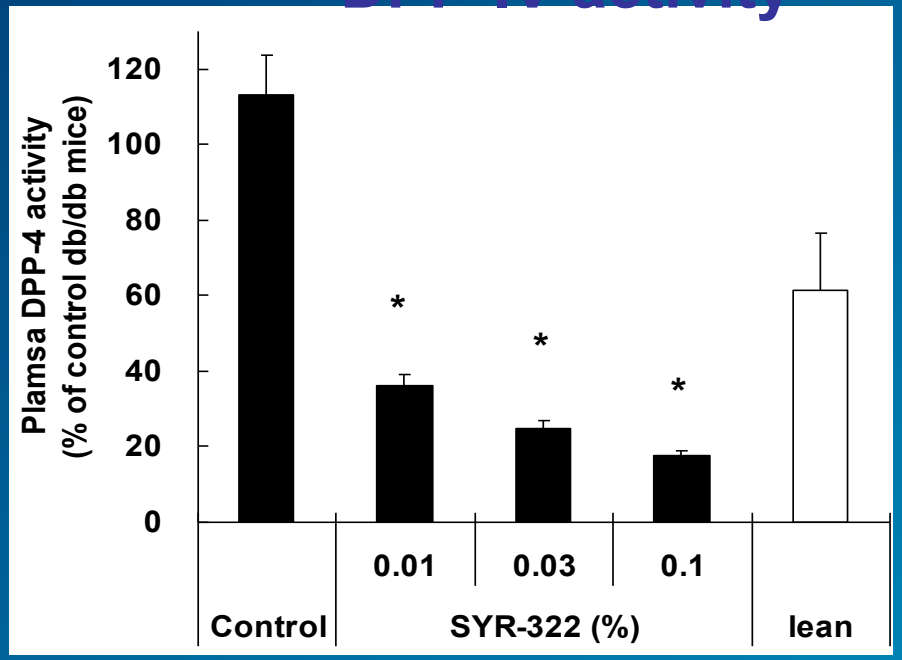
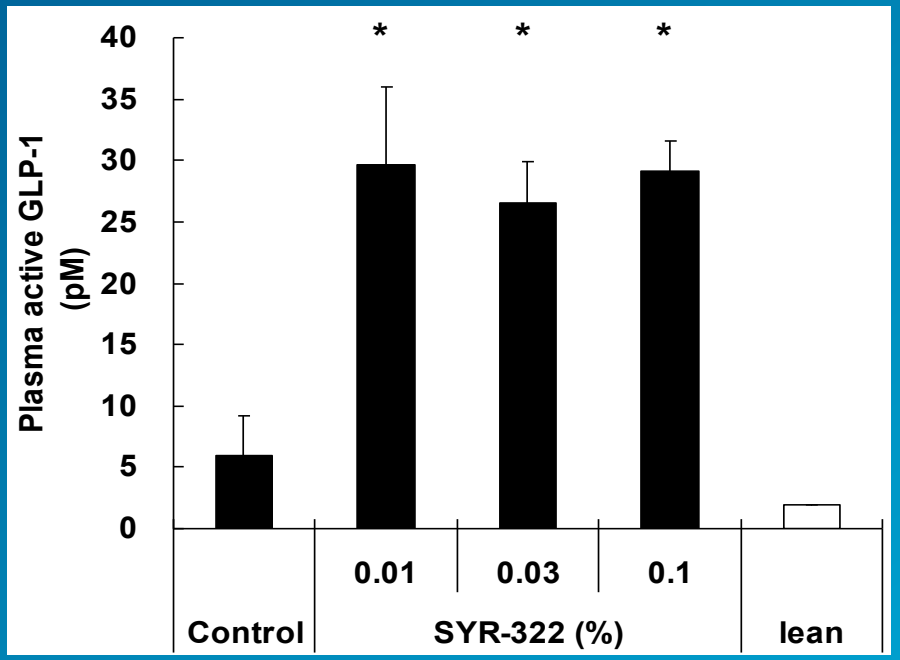
Alogliptin on DPP-IV and GLP-1 in *db/db* Mice

DPP-IV activity



GLP-1 level



Alogliptin dose-dependently inhibited plasma DPP-IV activity.

****p* ≤ 0.025 vs. control by one-tailed Shirley-Williams test.**

Alogliptin increased plasma active GLP-1 levels.

****p* ≤ 0.025 vs. control by one-tailed Williams' test.**

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Chronic (4 Week) Study in *ob/ob* (obese) mice

Study-1; Dose-dependent efficacy of Alogliptin

Study design				
Control	*ob/ob*	n=8	Untreated	
SYR-322	*ob/ob*	n=8	0.002% in diet	**(2.8±0.3 mg/kg/d)**
SYR-322	*ob/ob*	n=8	0.01% in diet	**(14.1± 0.8 mg/kg/d)**
lean	*?/+*	n=4		

Four weeks treatment of Alogliptin admixture with diet.

Study-2; High dose efficacy of Alogliptin

Study design				
Control	*ob/ob*	n=7	Untreated	
SYR-322	*ob/ob*	n=7	0.03% in diet	**(42.2± 4.0 mg/kg/d)**
lean	*?/+*	n=4		

Four weeks treatment of Alogliptin admixture with diet.

Mice; *ob/ob*/Crj and lean(Charles River Laboratories Japa

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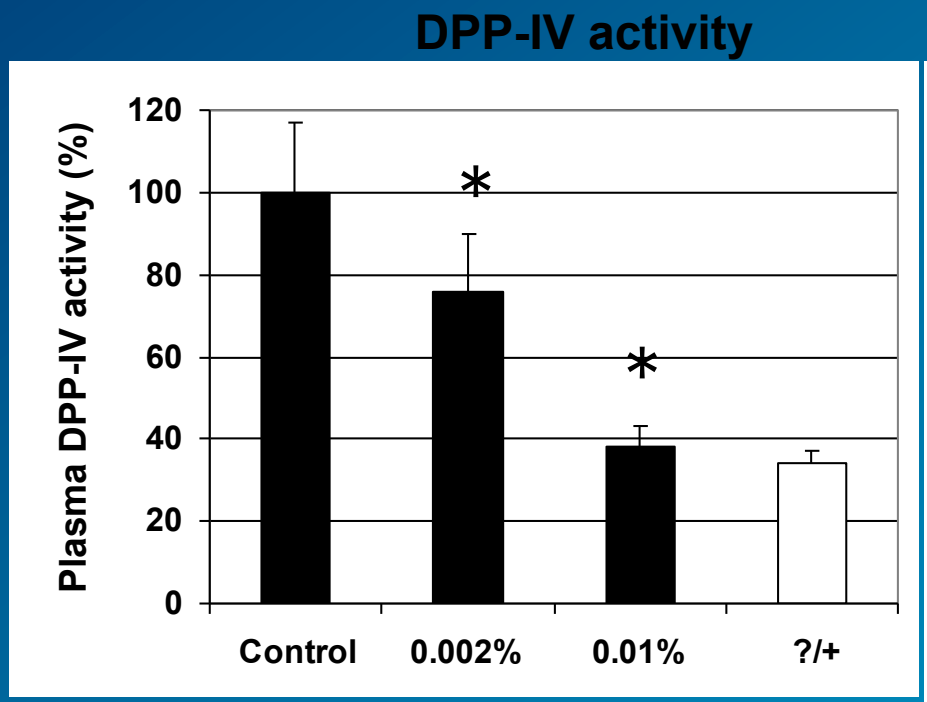
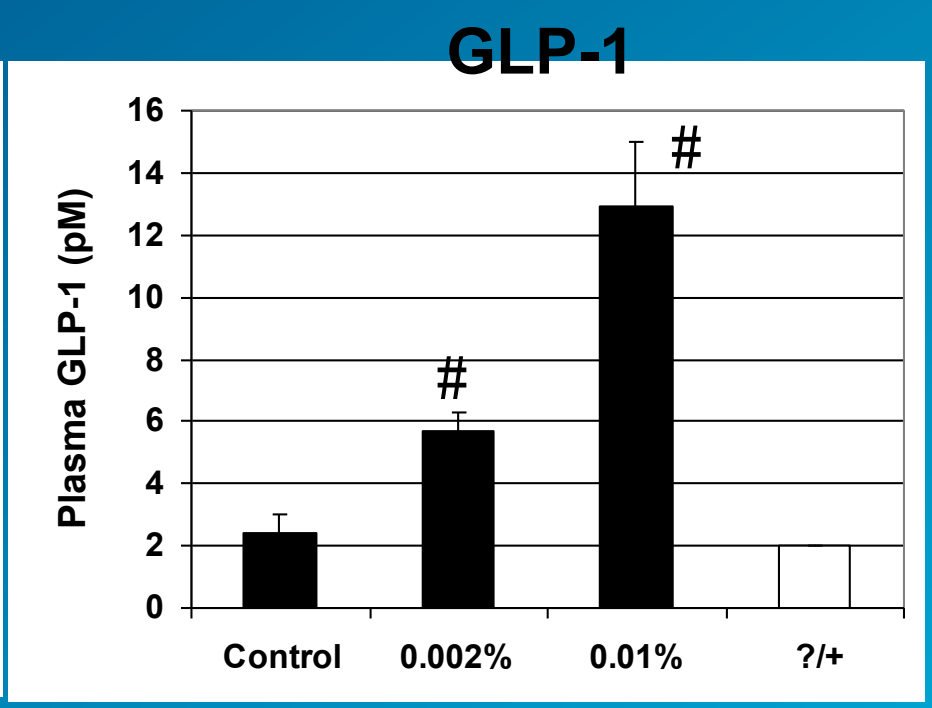
Plasma DPP-IV Activity and Active GLP-1 Levels after 4-week Treatment of Alogliptin in *ob/ob* Mice





Mean and SD, n=8
*p<0.05 vs control by one-tailed Williams' test.
#p<0.05 vs control by one-tailed Shirley Williams'test.

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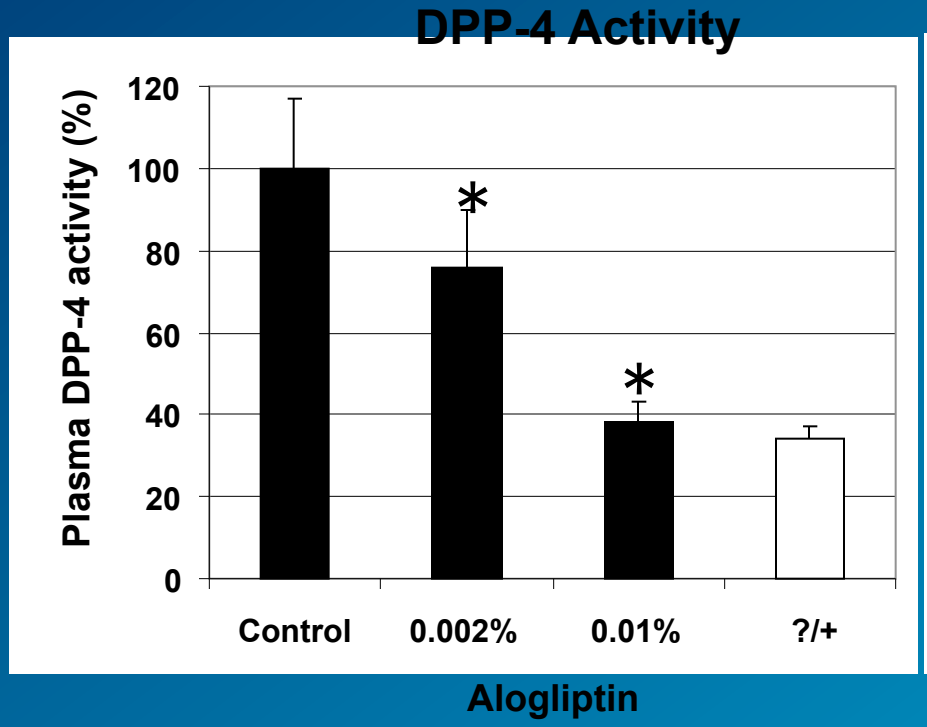
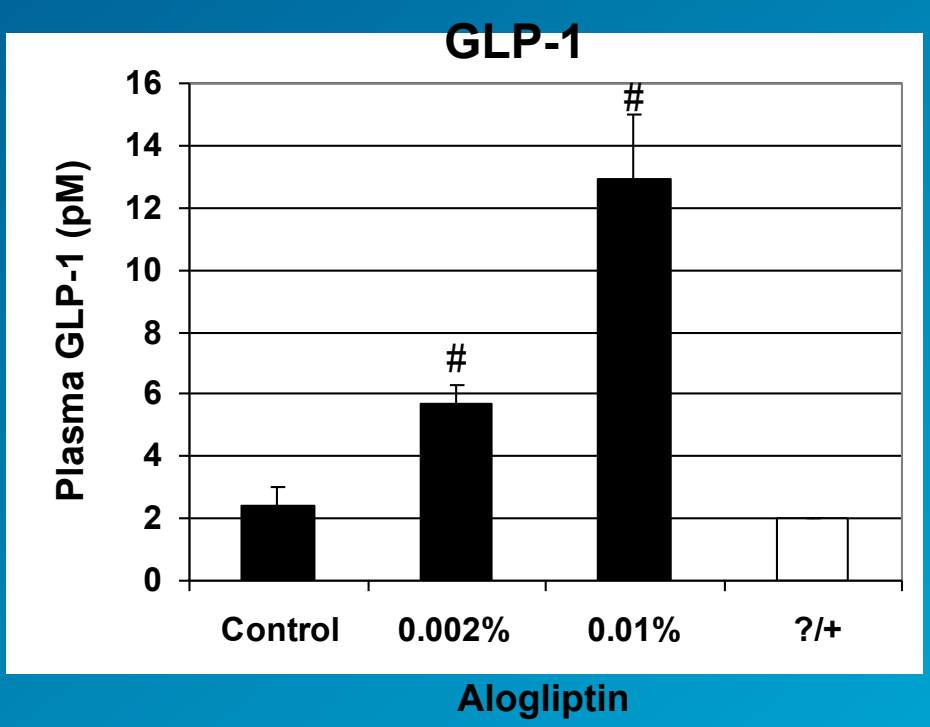
Alogliptin Reduces DPP-4 Activity and Increases GLP-1 Levels





ob/ob Mice
Mean and SD, n=8
*p<0.05 vs control by one-tailed Williams' test.
#p<0.05 vs control by one-tailed Shirley Williams' test.

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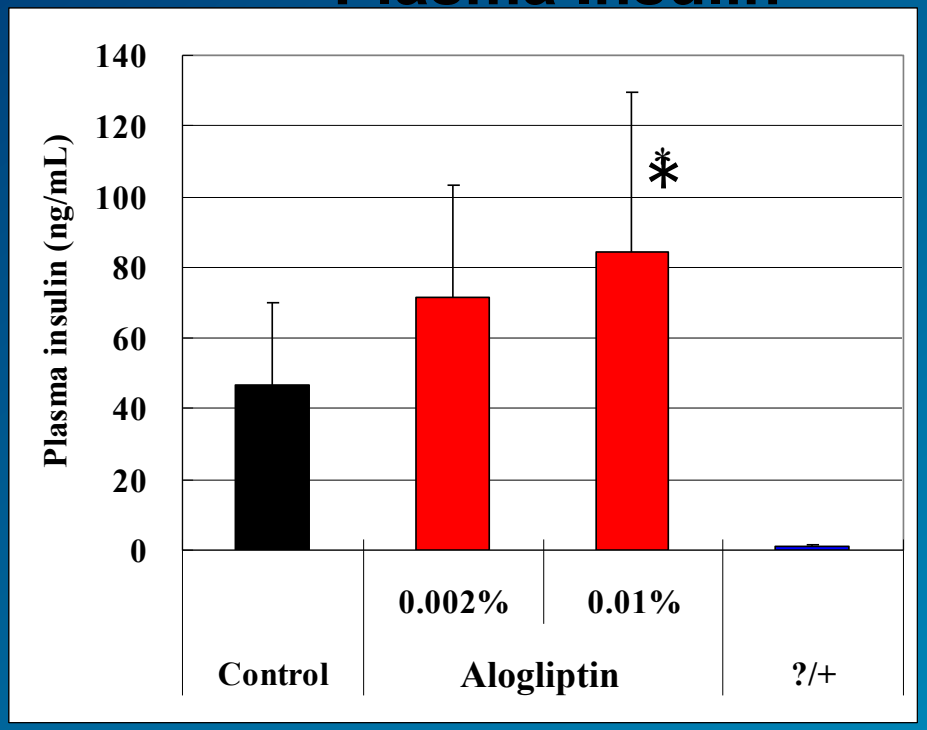
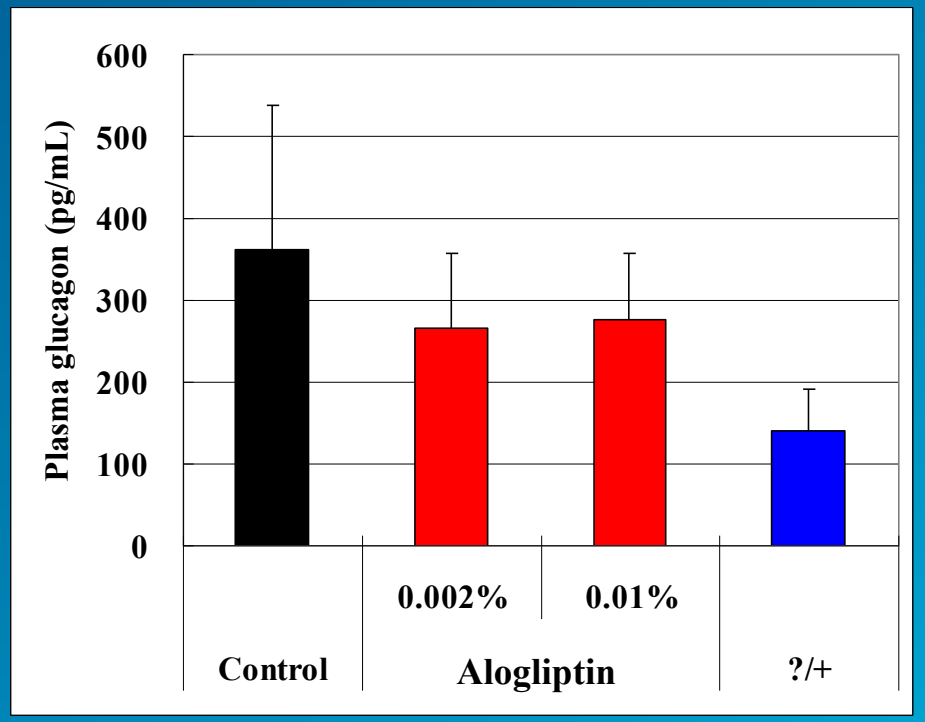
Alogliptin Increases Plasma Insulin and Decreases Plasma Glucagon

Plasma Insulin



Plasma Glucagon



Mean and SD, n=8
*p<0.05 vs control by one-tailed Williams' test.

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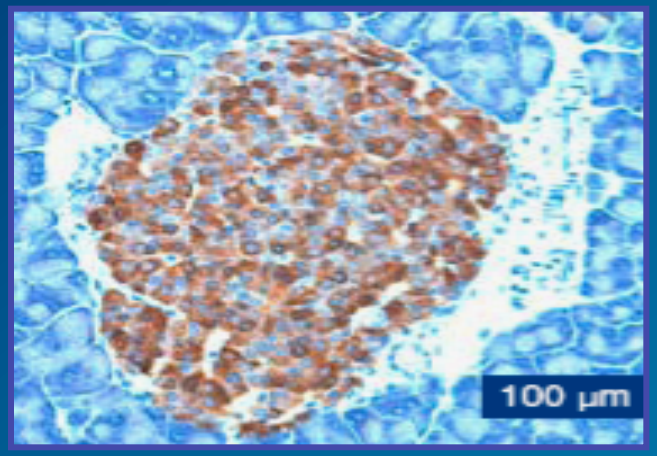
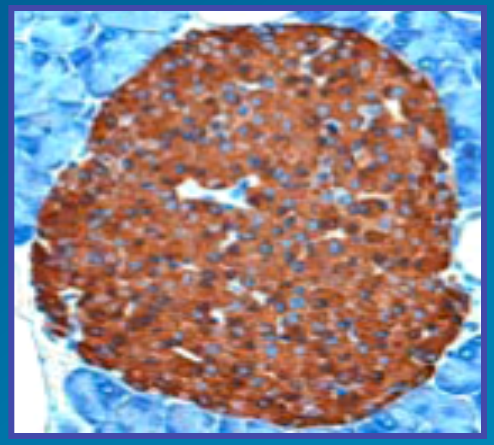
Pancreatic Insulin Content Restored with Drug

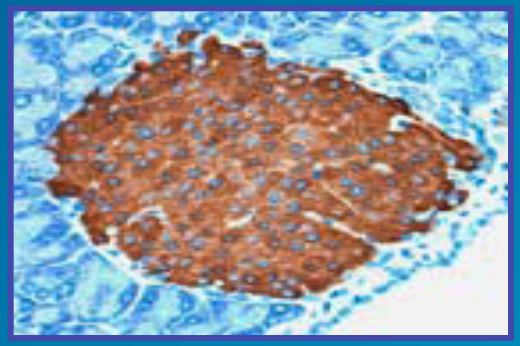
Control (Ob/Ob)



Alogliptin Treated (Ob/Ob)



Control



- Intense insulin staining was observed in islets of ob/ob mice treated with alogliptin
- Insulin staining in islets of alogliptin-treated ob/ob mice was comparable to that in vehicle-treated non-diabetic ?/+ mice

Moritoh et al, 511-P, ADA 2007

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Drug Metabolism & Pharmacokinetics

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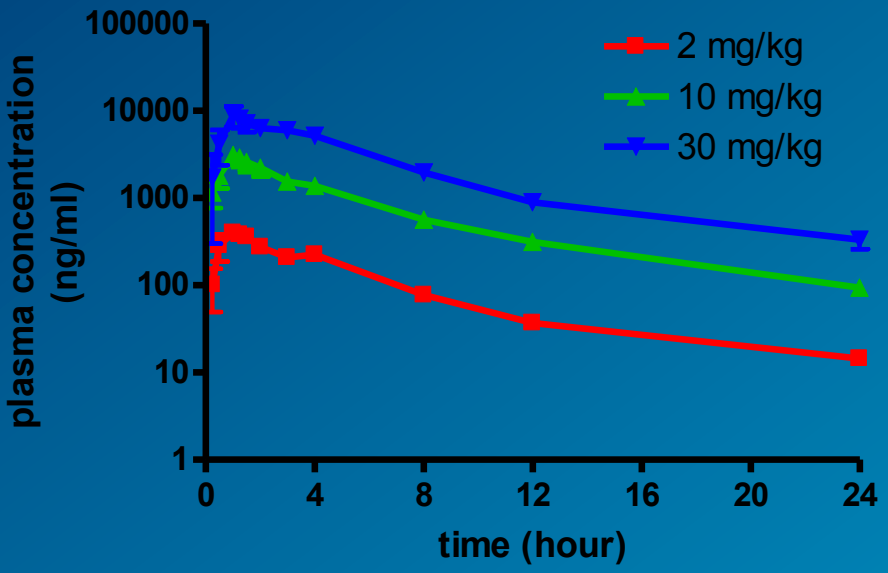
In Vivo Pharmacokinetic/Pharmacodynamic Profiles

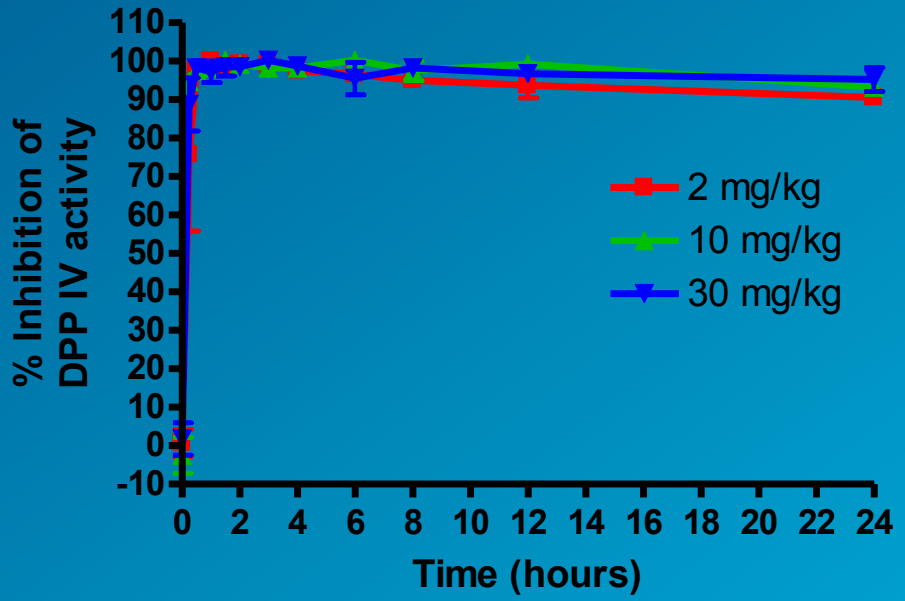
- **Sprague-Dawley rats**
- **Beagle dogs**
- **Cynomolgus monkeys**

Plasma Concentrations and DPP-IV Inhibition in Monkeys for Alogliptin (po)

Plasma concentrations



% Inhibition of DPP-IV activity



Dose linear pharmacokinetics

$T_{1/2}$ (oral) = 6 hours

F = >80%

Inhibition Initiated at 0.25 hours post dose

Maximum DPP-IV inhibition at 2 to 3 hours post dose (90% to 91%)

Inhibition still apparent at 24 hours post dose (81% to 84%)

Drug Metabolism Profile

- CYP Isoforms involved in metabolism
  - CYP-2D6 (*N*-demethylated metabolite)
  - CYP-3A4 also involved in metabolism
- CYP induction/inhibition
  - Minimal induction of CYP3A4/5 (up to 5.88X)
  - Minimal inhibition of CYP2D6 (27% at 100 µmol/L)
- Low protein binding
- No drug-drug interactions (in vitro) when co-administered with other diabetic agents

Pharmacokinetic Profile

Pharmacokinetic Parameters Following a Single Oral Dose

Parameter	Rats (20 mg/kg)	Dogs (2 mg/kg)	Monkeys (10 mg/kg)
Cmax	1,192	278	3,208
AUC(0-∞)	2,821	699	15,859
T1/2 (hours) (IV)	1.4	2.9	5.7
Tmax (hours)	1.7	0.75	1.0
F (%)	42	71	87
Excretion Route	Urine, feces	Urine, feces	--

Units: Cmax= ng/mL; AUC= ng·hr/mL

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Drug Safety Evaluation

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Alogliptin – Drug Safety Profile Overview

- Safety Pharmacology: No CNS, Cardiovascular or Pulmonary toxicities noted.
- Genetic Toxicology: Not mutagenic or clastogenic.
- Chronic Toxicology: doses up to 900 mg/kg (rat) and 200 mg/kg (dog)

Clinical Translation

Human Safety Margins

Endpoints From Oral Toxicity Studies	Dose (mg/kg/day)	AUC (ng·hr/mL)	Exposure Multiples* 12.5 mg	Exposure Multiples* 25 mg
6 Month Chronic Toxicity Study in Rats				
NOAEL	400	258,579	362	181
9 Month Chronic Toxicity Study in Dogs				
NOAEL	200	400,140	560	280

*Plasma $AUC_{0\text{-}24h}$ values determined based on data obtained in the multiple repeat dose (14 day) study in patients with type 2 diabetes mellitus.

NOAEL - No Observable Adverse Effect Level = nontoxic

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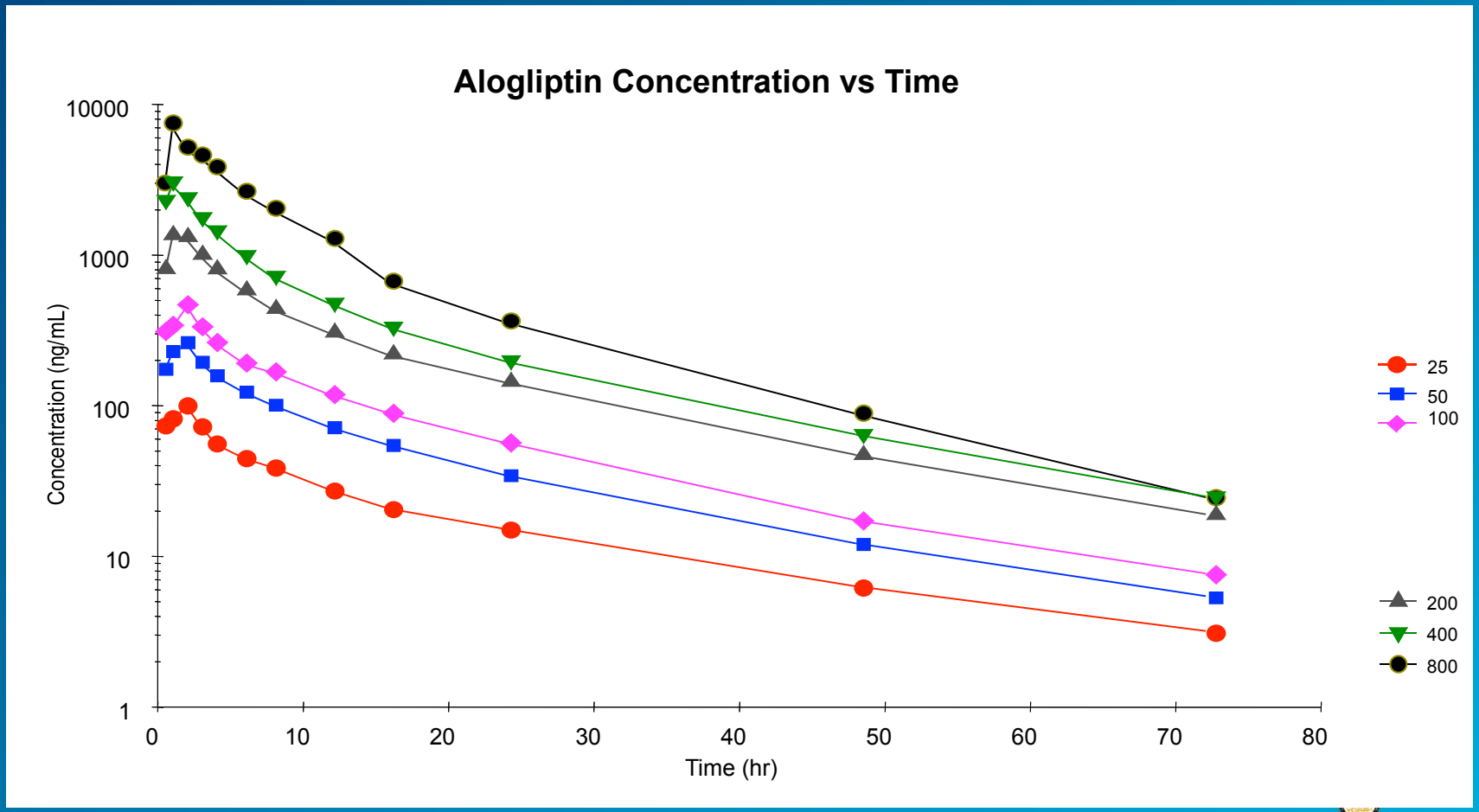
Single Dose in Healthy Volunteers: Pharmacokinetics



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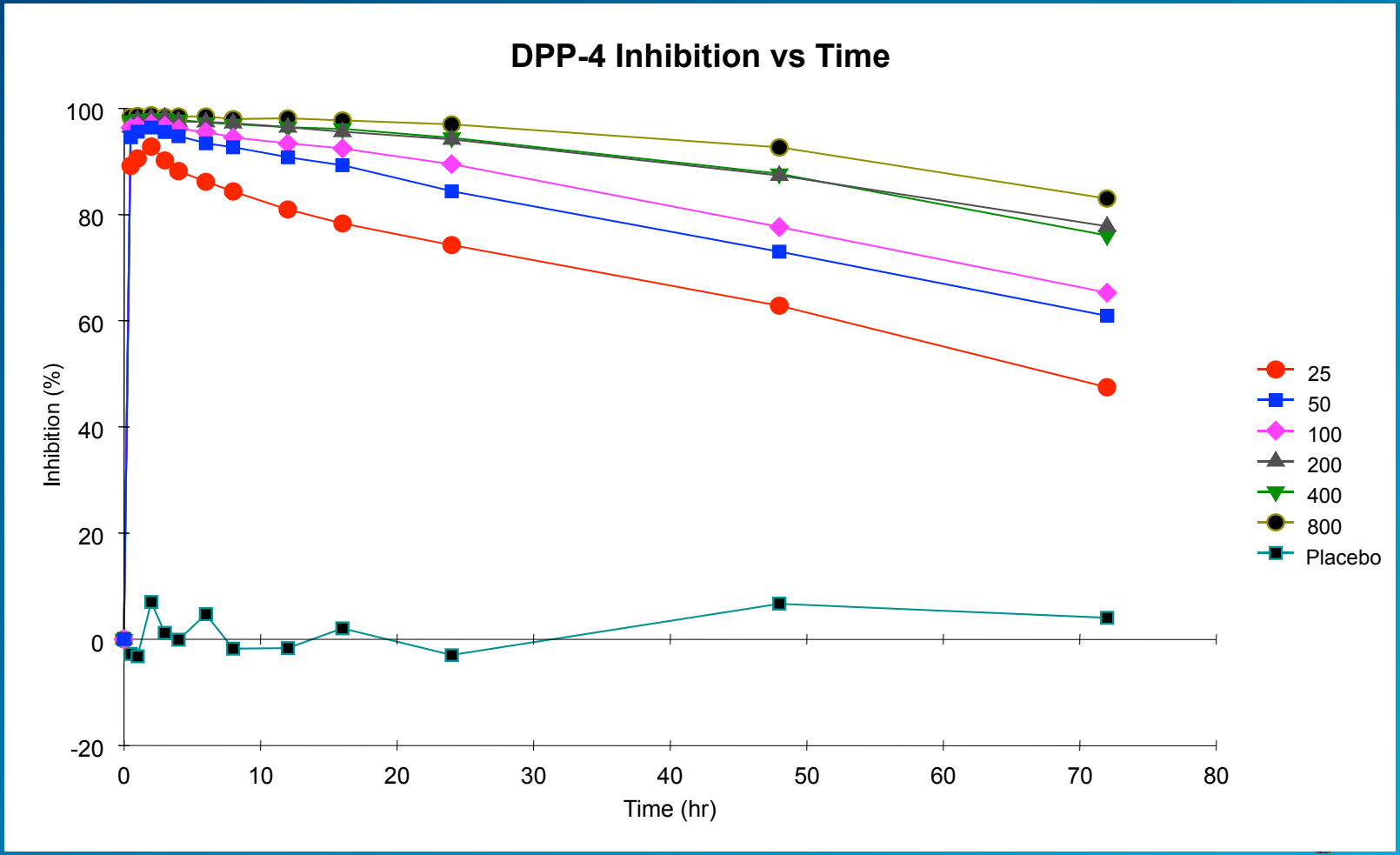
Single Dose in Healthy Volunteers: DPPIV Inhibition



Alogliptin Single Dose in Healthy Volunteers: Conclusions

- No dose-limiting adverse events
  - 25 mg to 400 mg to 800 mg
- Alogliptin was absorbed rapidly
- Total exposure (AUC) and peak exposure (C_{max}) increased with increasing dose
- Pharmacokinetics consistent with once daily dosing
- DPP-4 inhibition consistent with once daily dosing
- No significant metabolites
  - Plasma and urine concentrations of M-I (*N*-demethylated) and M-II (*N*-acetylated) metabolites were <5% of the parent drug

Thank you for your Attention

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