RANDOMIZED PLACEBO-CONTROLLED PHASE 1 TRIAL IN HEALTHY VOLUNTEERS INVESTIGATING SAFETY, PK AND PD OF EXOIL-12 – A NOVEL ENGINEERED EXOSOME THERAPEUTIC CANDIDATE

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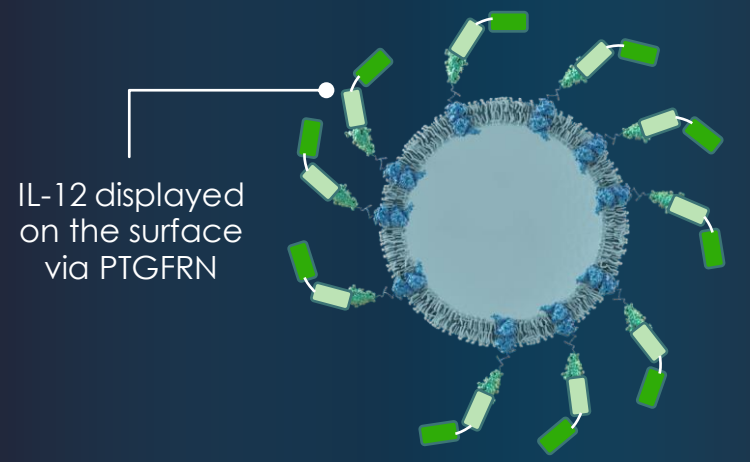
Introduction

- IL-12 has documented anti-tumor activity in humans[1]
- Systemic toxicity of rIL-12 has prevented development as a drug[2]
- exoIL-12™ is a novel, engineered-exosome that displays functional IL-12 on the surface and is designed for local intra-tumoral administration and retention.
- Alternative delivery and dosing regimes (*e.g.*, AAV, electroporation) result in inconsistent doses and systemic release of IL-12
- We engineered IL-12 onto the exosome surface to limit systemic exposure and maximize local pharmacology within the tumor microenvironment

exoIL-12™



[1] Blood. 1997 1;90(7):2541-8.
[2] Cancer Immunol Immunother. 2014 63:419–435.

Objectives

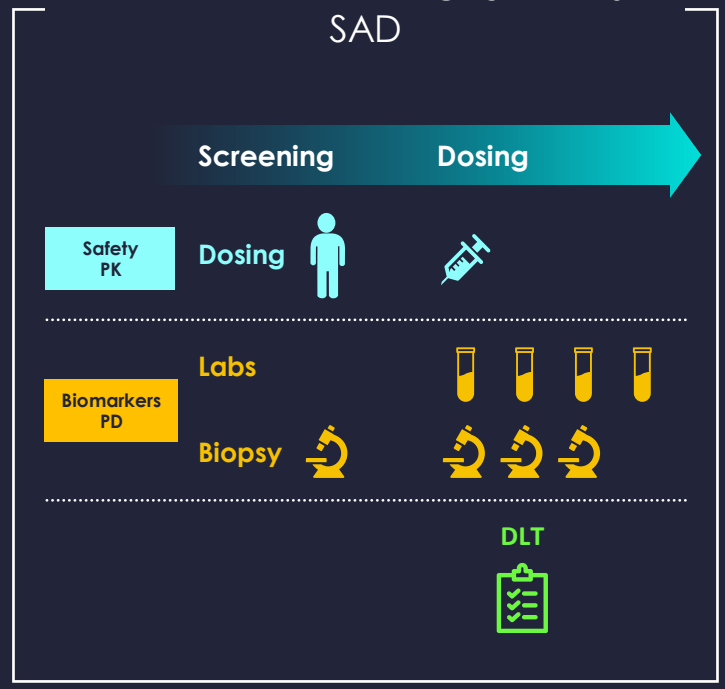
1. Confirm unique target product profile of exoIL-12:
   - No systemic IL-12 exposure
   - Local retention at injection site
   - Favorable safety and tolerability profile as compared to historical data in rIL-12
   - Local and prolonged pharmacodynamic effect

2. Identify optimal dose and dosing regimen for Part B of the Phase 1 study in patients with Stage IA-IIB Cutaneous T-cell Lymphoma (CTCL)

Study Design

- A Phase 1 study in 2 parts:
  - Part A was in 25 healthy volunteers
  - Part B is an open-label design in patients with Stage IA-IIB CTCL

- Part A:
  - Randomized, placebo-controlled, double-blind single ascending dose (SAD) trial
  - A total of 5 dose cohorts were completed: 0.3, 1.0, 3.0, 6.0 and 12.0 µg
  - All injections were administered in the right thigh
  - PK blood samples: Pre-dose, 1, 2, 4, 6, 8, 12, 24, 48hrs and Days 8, 15, 22 and 29 post-dose



Sample Timepoints, Skin Punch Biopsy Procedure & PD

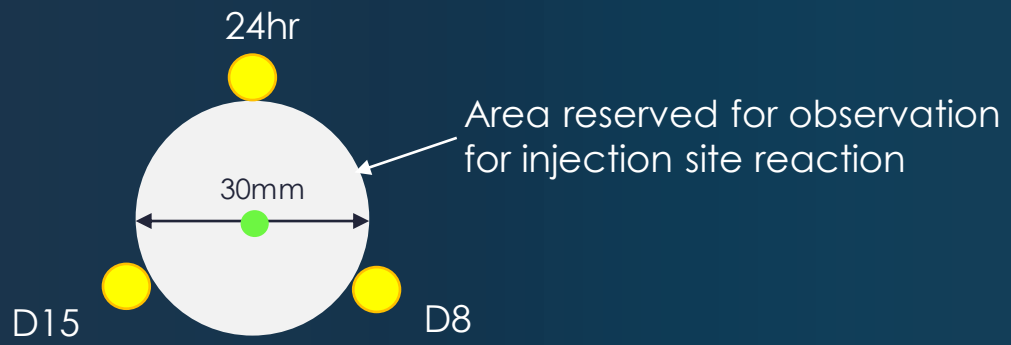
Plasma

Skin

Biopsy core (●) taken using Stiefel Biopsy Punch - 3mm and scalpel.

Penetrating epidermis, dermis and reaching upper sub-cutaneous tissue.

Pre-treatment



● Injection site of exoIL-12
(variable dose, fixed volume of 2ml)

exoIL-12

T cells and NK cells via IL-12 receptor

Interferon-gamma-induced protein-10 (IP-10)

Study Population Demographics

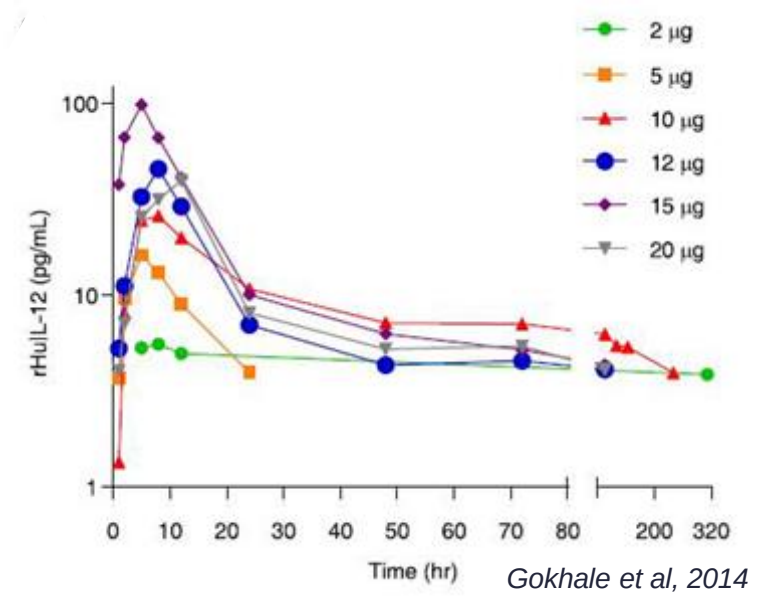
	Age		Race		Weight (kg)		Height (cm)		BMI	
All N=25	27 (18; 40)		A: 4/25 (16%) B: 6/25 (24%) C: 15/25 (60%)		69.7 (55; 83)		177.2 (167; 190)		22.1 (18.3; 24.9)	
	exoIL-12	Placebo	exoIL-12	Placebo	exoIL-12	Placebo	exoIL-12	Placebo	exoIL-12	Placebo
Cohort 1 – 0.3 µg N=5	32 (22; 37)	26 (25; 27)	C (2), B (1)	C (2)	70 (67; 73.8)	70.5 (65.4; 75.7)	177.3 (176; 178)	177 (171; 183)	22.3 (21.6; 23.3)	22.5 (22.4; 22.6)
Cohort 2 – 1.0 µg N=5	23 (19; 29)	19 (19; 19)	B (3)	C (2)	67.8 (57.2; 77.2)	80.6 (78.1; 83.2)	177 (168:185)	190 (190; 190)	21.6 (20.3:22.6)	22.3 (21.6; 23)
Cohort 3 – 3.0 µg N=5	20 (18; 22)	26 (20; 31)	C (2), A (1)	A (2)	69.4 (60.7; 82.8)	65.3 (54.9; 75.7)	176.3 (169; 183)	175 (173; 177)	22.2 (20.7; 24.7)	21.3 (18.3; 24.2)
Cohort 4 – 6.0 µg N=5	31 (24; 36)	27.5 (21; 34)	A (1), B (1), C (1)	C (2)	70.3 (56.1; 79.7)	71.6 (68.7; 74.5)	179.7 (170; 190)	178 (176; 180)	21.6 (19.4; 23.4)	22.6 (22.2; 23)
Cohort 5 – 12.0 µg N=5	32.7 (25; 40)	28 (21; 35)	B (1), C (2)	C (2)	64.3 (61.9; 68.5)	69.9 (67.7; 72)	173 (167; 176)	170.5 (170; 171)	21.6 (20; 24.6)	24.1 (23.2; 24.9)

Numbers listed as Average (Min; Max)
A: Asian, B: Black or African American, C: Caucasian

No Systemic IL-12 Exposure and No Treatment-Related AEs with exoIL-12

rIL-12

Plasma IL-12 following rIL-12

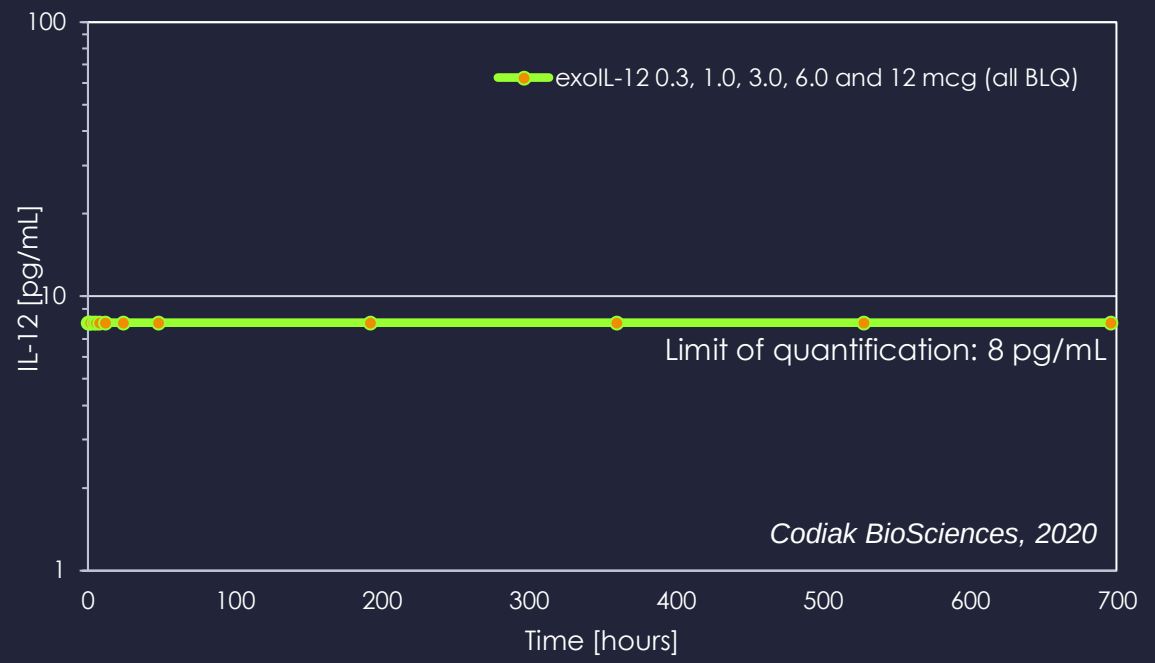


Tolerability Summary

- SC SAD of rIL-12 from 2 – 12 µg
- Dose dependent treatment related AE:
  - Chills
  - Fatigue
  - Myalgia
  - Back pain
  - Fever
  - Dizziness
  - Headache

exoIL-12

Plasma IL-12 following exoIL-12



Tolerability Summary

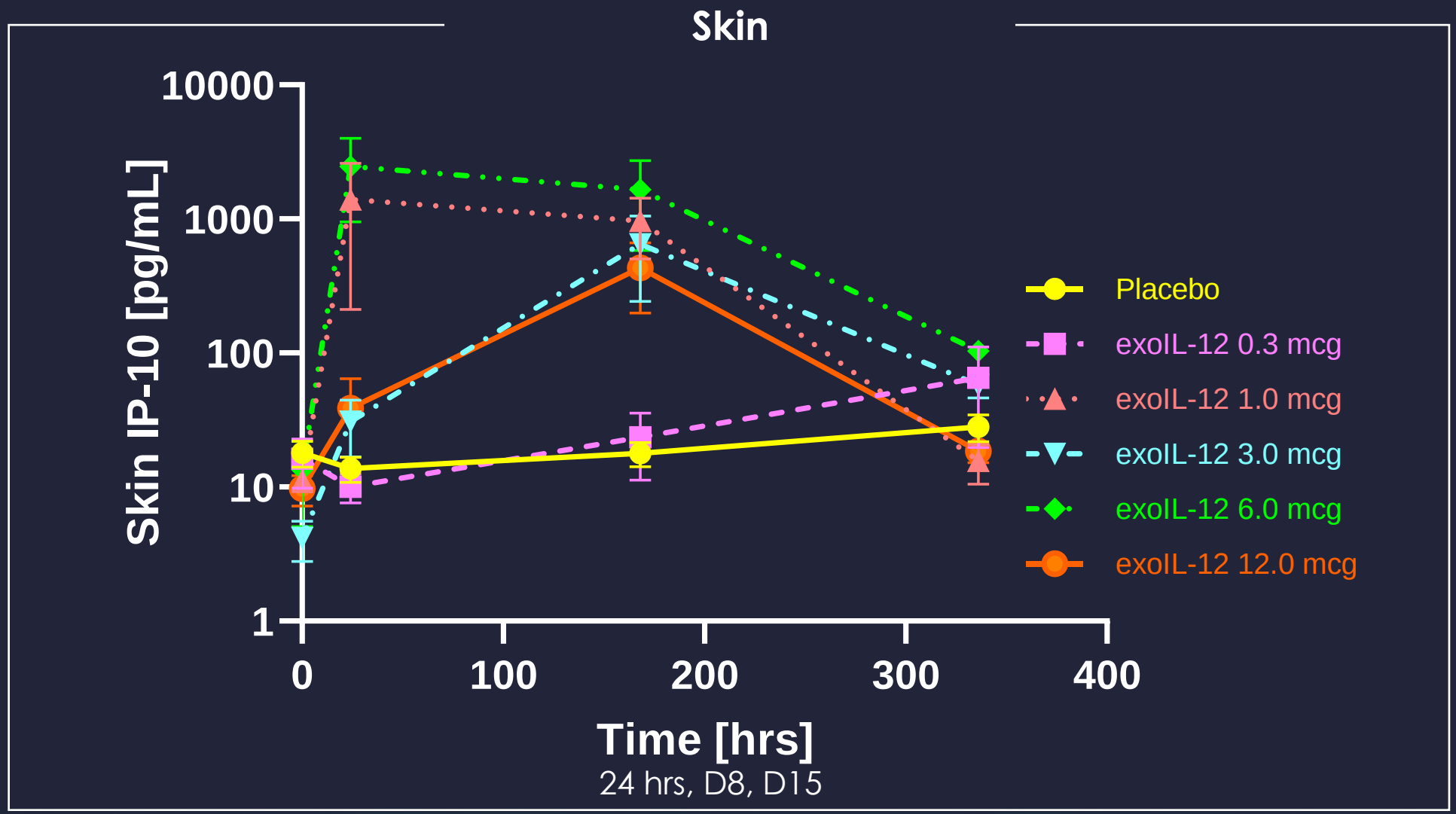
- SC SAD of exoIL-12 from 0.3 – 12 µg
- No treatment-related AEs

Adverse Events Table – No drug-related AEs

	AE description		IMP related	Grade 1		Grade 2-4	
All subjects N=25	Stress Viral upper respiratory tract infection Gastroenteritis Rash (left leg) Cold sores Headache Pseudo folliculitis barbae Hand injury		None	All		0	
	exoIL-12	Placebo		exoIL-12	Placebo	exoIL-12	Placebo
Cohort 1 – 0.3 µg N=5	Stress, Viral upper respiratory tract	0	None	Stress, Viral upper respiratory tract	0	0	0
Cohort 2 – 1.0 µg N=5	Gastroenteritis	0	None	Gastroenteritis	0	0	0
Cohort 3 – 3.0 µg N=5	Rash (left leg)	Cold sore, headache	None	Rash (left leg)	Cold sore, headache	0	0
Cohort 4 – 6.0 µg N=5	0	0	None	0	0	0	0
Cohort 5 – 12.0 µg N=5	Pseudo folliculitis barbae, Hand injury	0	None	Pseudo folliculitis barbae, Hand injury	0	0	0

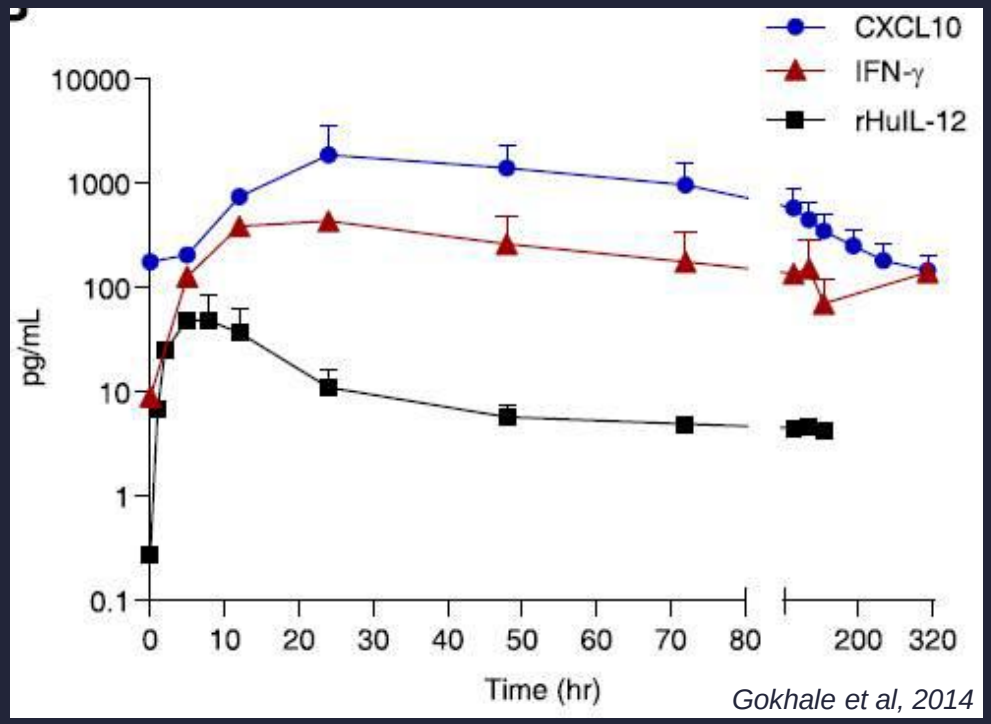
IMP: Investigational Medical Product

Potent, Durable IP-10 Effects in Injected Skin Following exoIL-12



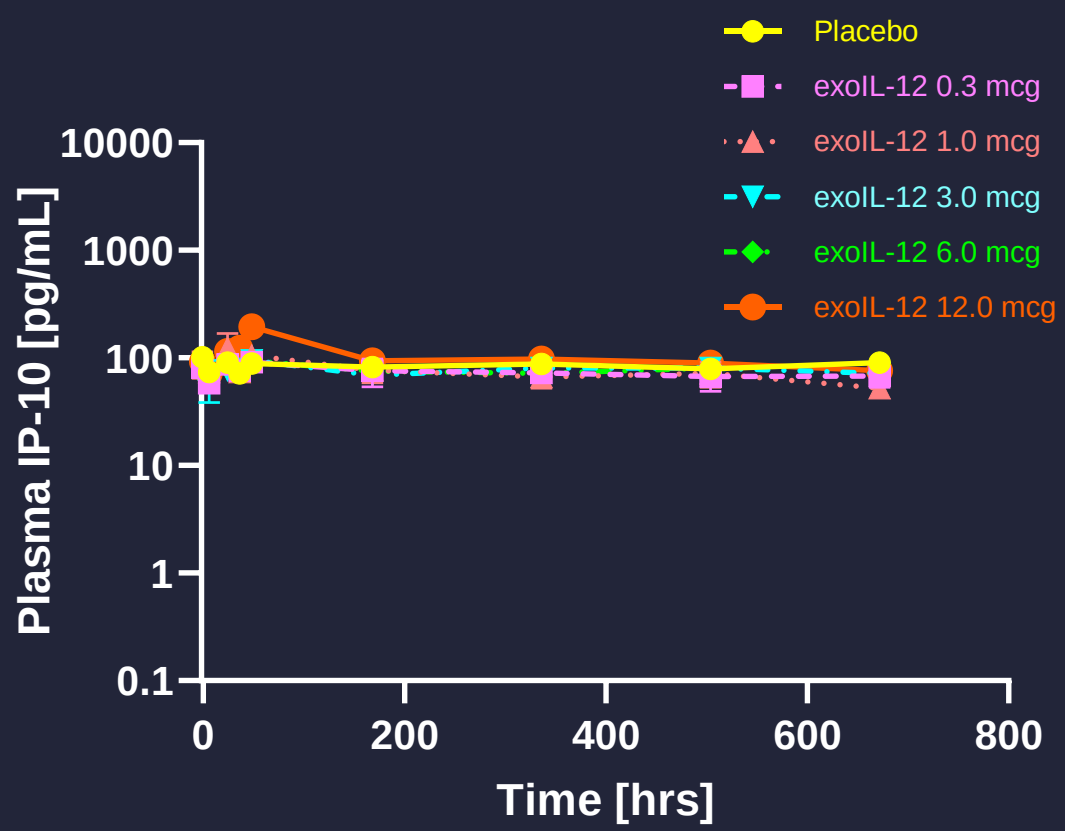
No **Plasma IP-10** Generation of exoIL-12 at 0.3 to 6.0 µg

rIL-12 at 12.0 µg



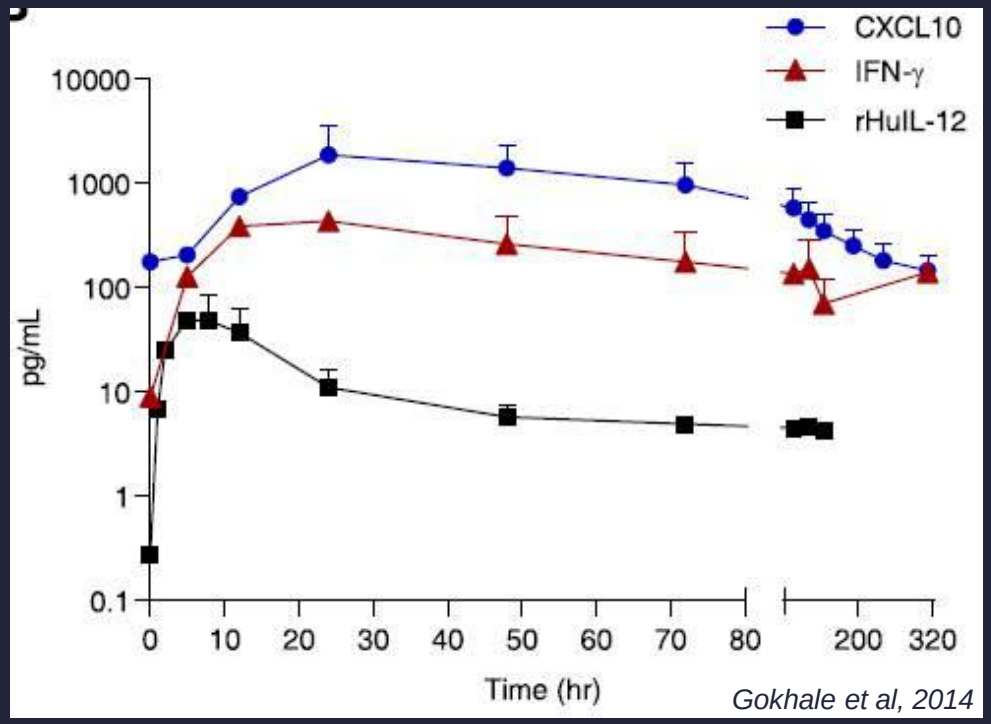
Gokhale et al, 2014

exoIL-12



No **Plasma IFN-γ** Generation of exoIL-12 at 0.3 to 12.0 µg

rIL-12 at 12.0 µg



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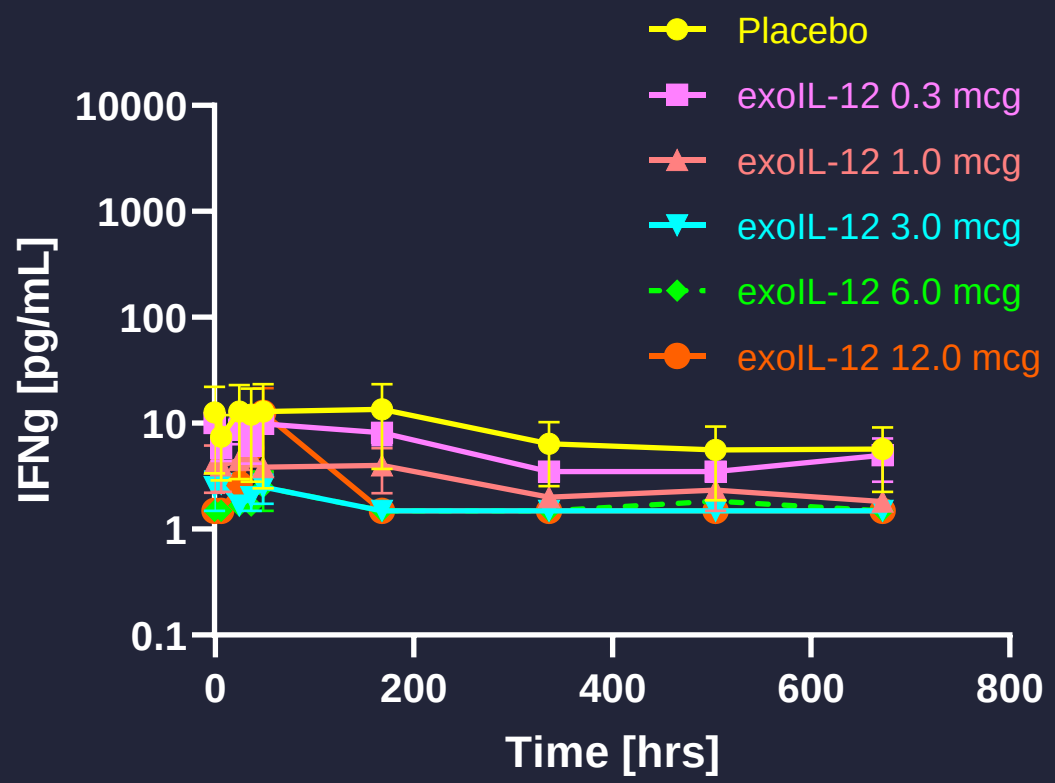
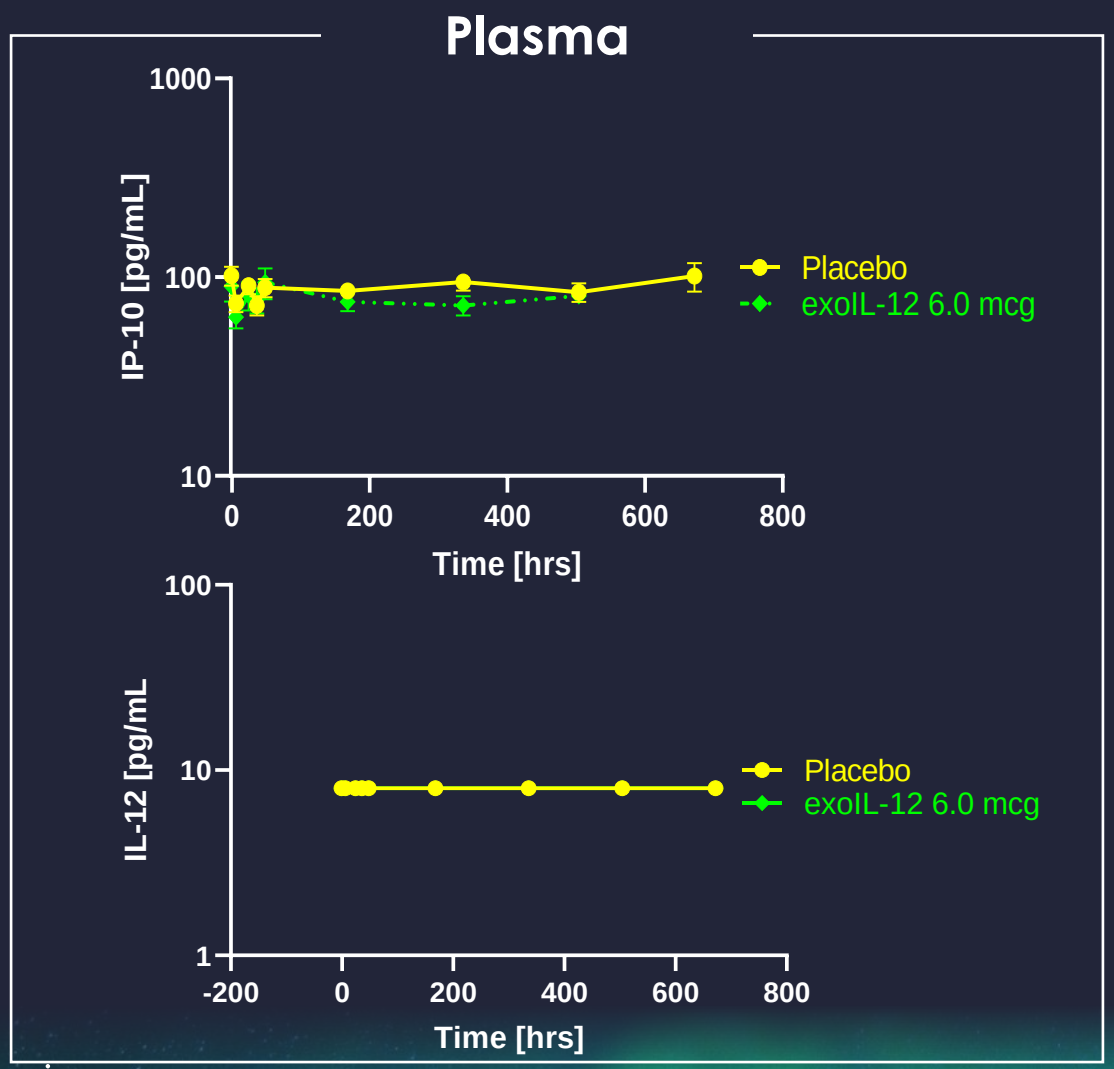
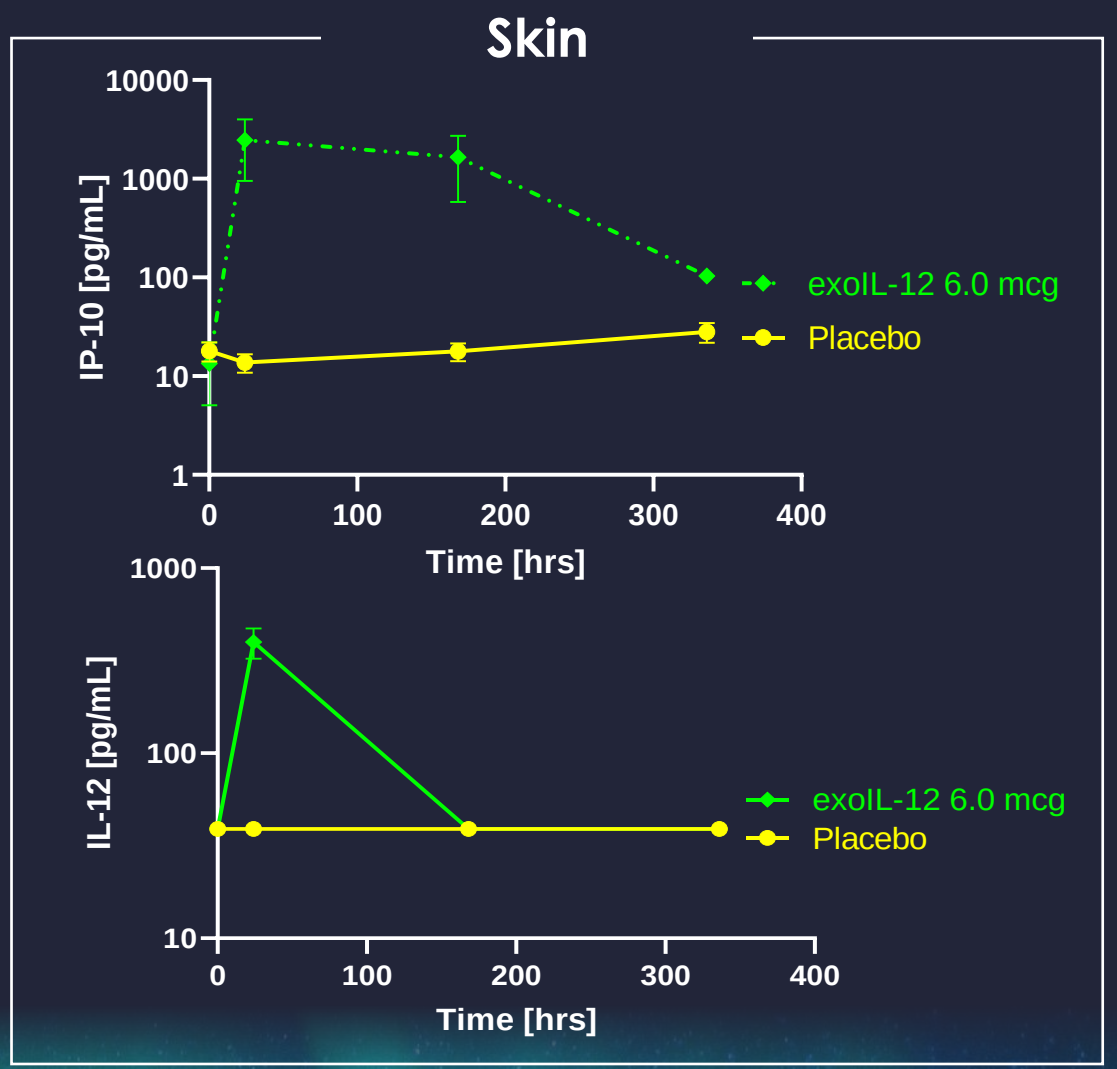


The 6.0 µg Dose is Optimal and Meets all Pre-Specified Criteria





Data Confirm Distinctive Profile of exoIL-12

- exoIL-12 was well tolerated at SADs from 0.3 to 12.0 µg in healthy volunteers
- No systemic exposure of IL-12 – direct contrast with comparable dosages of rIL-12
- exoIL-12 detectable in skin at 6.0 µg – data supportive of retention at injection site
- exoIL-12 at 1.0 to 12.0 µg showed potent skin IP-10 with highest levels at 6.0 µg
- Slight increase in plasma IP-10 on Day 3 with12.0 µg
- Data support Part B starting dose of 6.0 µg every other week
- Provides validation of engEx Platform for engineering exosome therapeutic candidates