sirnaomics
Advancing RNAi Therapeutics

Sirnaomics Ltd. (2257.HK)

Meeting with investors – STP705 Fat Remodeling interim results

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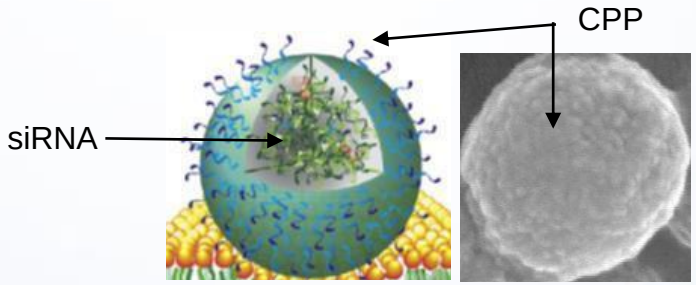
Two Proprietary Delivery Platforms and Therapeutic Areas

1 PNP Platform (Clinical Stage)

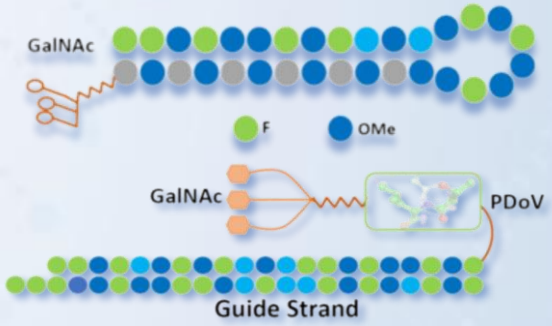


HKP and HKP(+H) are well suited for siRNA Therapeutics or mRNA Therapeutics and Vaccine Deliveries

2 GalNAc Platform (Clinical Candidate)

GalAhead ™

PDoV-GalNAc ™



mRNA | **Cancer** | **Fibrosis Diseases** | **Viral Infections** | **Liver Metabolic Diseases**

- Vaccine
  Neoantigen Vaccine
  Protein Replacement
  mRNA Antibody
- NMSC (isSCC, BCC)
  Liver Cancer
  Lung Cancer
  Pancreatic Cancer
  Colon Cancer
- Skin Scar, Keloid
  Liver Fibrosis
  Lung Fibrosis
  Kidney Fibrosis
- Influenza
  SARS-CoV2
  HBV
  HPV
- Anti-Coagulant
  LDL Deregulation
  High Blood Pressure
  Compliment Disease

RNAi

Polypeptide Nanoparticle Platform for RNA Delivery

Backbone PNP delivery platform is a potential game changer

Significant advantages against existing platforms

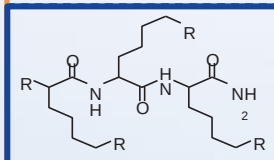
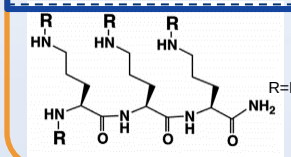
High delivery efficiency
for both local and systemic applications

Validated safety
tested locally in human and systemically in NHP

High packaging efficiency
>97% loading, can carry multiple RNA molecules

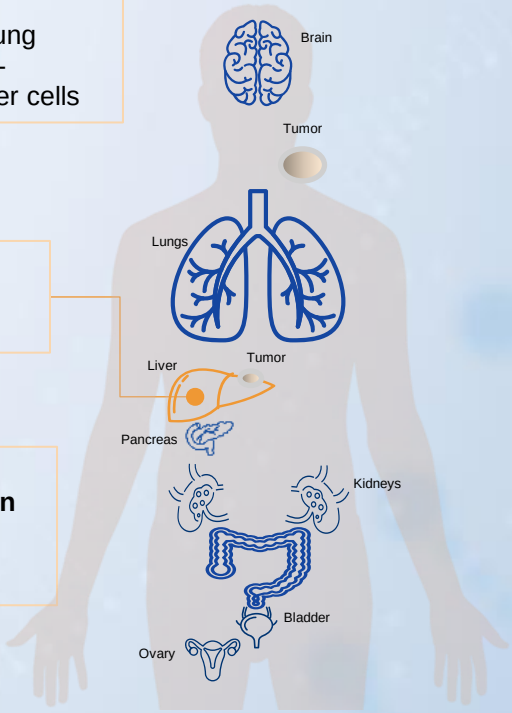
Simple and stable Formulation
easy synthesis process, no cold chain storage required

Highly efficient for broad applications using different encapsulating peptides

HK Peptides		Applications	siRNA	mRNA
KHHHKHHHKHHHKHHHK	=	H3K	√	
 R=KHHHKHHHKHHHKHHHK	=	H3K4b, brunched	√ (local)	
 R=KHHHKHHHKHHHKHHHK	=	H3K(H)4b, branched	√ (systemic)	√

siRNA is much more than for hepatocytes of the liver

- ✓ **A wide range of organs targeted:** Tumor cells, lung cells, and non-hepatocyte liver cells
- ✓ **Multiple** liver cell types targeted
- ✓ **Multiple administration routes:** IV, IT



*The organs shown in the picture are targeted

- **Current Clinical Uses:** isSCC (Ph IIb), BCC (Ph II), Keloid (Ph 1/2), HTS (Ph IIa), liver cancer(basket) (Ph 1), Solid tumors (Ph I)
- **Planned Clinical Uses:** Solid tumors, liver cancer, Cholangiocarcinoma, pancreatic cancer, Colorectal Cancer, NSCLC, cSCC, lung fibrosis, liver fibrosis, etc.

Prioritized Product Pipeline Advancing Oncology Programs

	Candidate	Gene Targets	Indications	Delivery Platform	Rights	Status
Oncology	STP705	TGF-β1/COX-2	isSCC	PNP-IT	Global	Communicating with FDA re late-stage trial
					Global	Data readout in Q2 2023, Communicating with FDA re late-stage trial
			BCC		Global	
	STP707	TGF-β1/COX-2	Multiple solid tumors	PNP-IV	Global	Interim data released in Q4 2022
	Three Other Early-Stage Assets			PNP	Global	
Medical Aesthetics	STP705	TGF-β1/COX-2	Fat remodeling	PNP subcutaneous	Global	Interim Data readout
Antiviral	STP702	M1/PA	Influenza	Airway / PNP-IV	OL China	Continue partnership
	RV-1730[1]	SARS-CoV-2	Covid-19 vaccine	LNP Intramuscular	Global	IND approved by FDA
GalAhead™	STP122G	Factor XI	Anticoagulation / Thrombosis	GalAhead™ subcutaneous	Global	First Patient In
	STP125G	ApoC3	Hypertriglyceridemia		Global	IND in 2023
	STP144G	Complement Factor B	Complement-mediated diseases		Global	IND in 2024
	Seven Other Early-Stage Assets				Global	

Abbreviations:
isSCC= cutaneous squamous cell carcinoma in situ; BCC= basal cell carcinoma; PNP = our polypeptide nanoparticle (PNP) RNAi delivery platform; PNP-IT = PNP platform formulated for intratumoral administration; PNP-IV = PNP platform formulated for intravenous administration; PNP-ID = PNP platform formulated for intradermal administration, GalAhead = our GalNAc RNAi delivery platform that conjugates GalNAc moieties to RNAi triggers; LNP = lipid nanoparticle (LNP) formulation for delivery of mRNA; OL China = out-licensed mainland China, Hong Kong, Macau, and Taiwan rights under agreement with Walvax but we retain the rights for rest of the world;

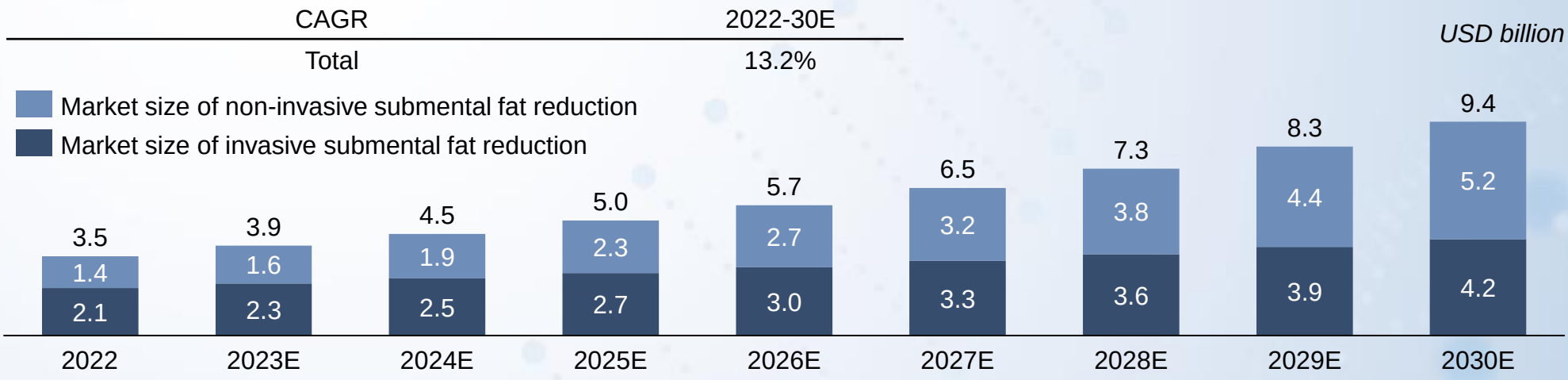
Note:
1. Research and development conducted by our subsidiary RNAimmune.

This study is our first attempt to apply RNAi therapeutic candidates to localized fat remodeling, and this development will open up new therapeutic areas for our pipeline in medical aesthetics

Market Size of Submental Fat Reduction

Global market increases from USD 3.5b in 2022 to USD 9.4b in 2030

Global market size of submental fat reduction treatment, 2022-2030



- According to Data Bridge Market Research, the size of the global submental fat reduction market is **US$3.5 billion in 2022**, which is estimated to grow at a **CAGR of 13.2%** to **US$9.4 billion in 2030**.
- According to Data Bridge Market Research, the size of the submental fat reduction market in North America is **US$695.5 million in 2022**, which is projected to grow at a **CAGR of 13.9%** to **US$1.9 billion in 2030**.
- According to a survey of conducted in 2013, the plastic surgeons revealed that liposuction was used in 81% of cases for submental fat reduction, followed in popularity by radiofrequency treatment in 7% and laser liposuction in 4%. While liposuction may provide the most dramatic and reliable treatment result, many patients are **reluctant to undergo liposuction** because of the **associated ecchymosis, skin laxity, surgical recovery time, and post-surgical elevations in blood pressure**.
- Since the approval of **non-invasive treatments**, such as Kybella, non-invasive procedures are on a dramatic rise. Currently, non-invasive procedures play an important role in the submental fat reduction market, and they are **projected to gain more market share** in the future.

Source: from CIC

Non-invasive market expected to outpace device market

Market for Fat Reduction in Different Parts of Body

Market potential for different parts of the body

Abdomen/Flanks
12.0MM

Inner Thighs
5.0MM

Outer Thighs
4.0MM

Buttocks
4.0MM

Arms
4.0MM

Submentum
3.0MM

Gynecomastia
0.5MM

Total U.S. Potential
32.5MM

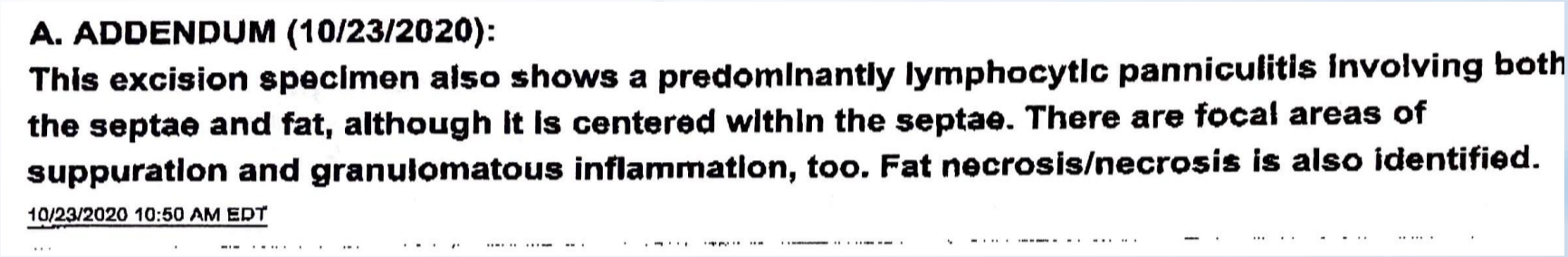
Source: Rabin Research Report(n.d.) interview of 1,076 US men and women. Retrieved from https://10xbio.com/wp-content/uploads/2019/05/10xBioNonConfidential51619.pdf

Interim Data from Phase I Clinical Trial of STP705 for Medical Aesthetic

Unexpected Findings in a Clinical Trial of isSCC

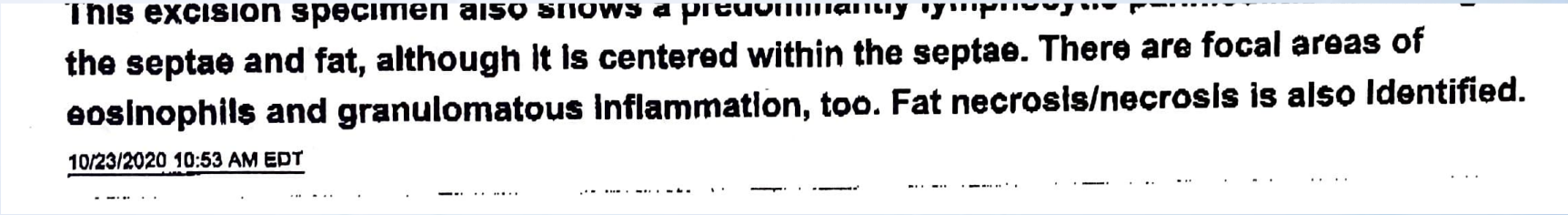
In the isSCC clinical phase 2a trial we found that at 120µg in the high dose group, narrowing of the subcutaneous fat layer and visible adipose tissue necrosis were observed

Subject 1: Right forearm



A. ADDENDUM (10/23/2020):
This excision specimen also shows a predominantly lymphocytic panniculitis involving both the septae and fat, although it is centered within the septae. There are focal areas of suppuration and granulomatous inflammation, too. Fat necrosis/necrosis is also identified.
10/23/2020 10:50 AM EDT

Subject 2: Right clavicle



This excision specimen also shows a predominantly lymphocytic
the septae and fat, although it is centered within the septae. There are focal areas of eosinophils and granulomatous inflammation, too. Fat necrosis/necrosis is also identified.
10/23/2020 10:53 AM EDT

When the world gives you Lemons, make Lemonade!

STP705 Fat Reduction in a Minipig Model Experiment

Results

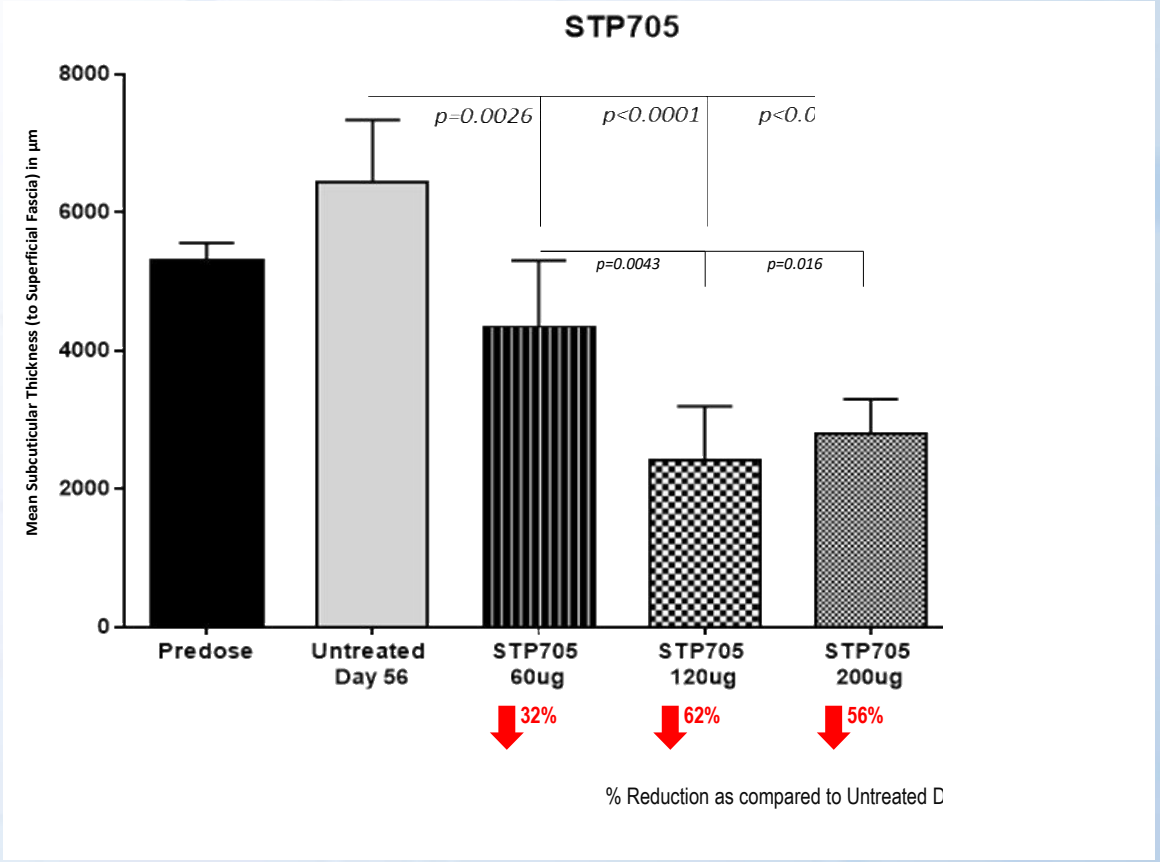
Dosing:

- **Once weekly for three weeks STP705**

Endpoint:

- **subcuticular fat measurements**

STP705 demonstrated significant reduction in mean subcuticular thickness in this POC porcine model



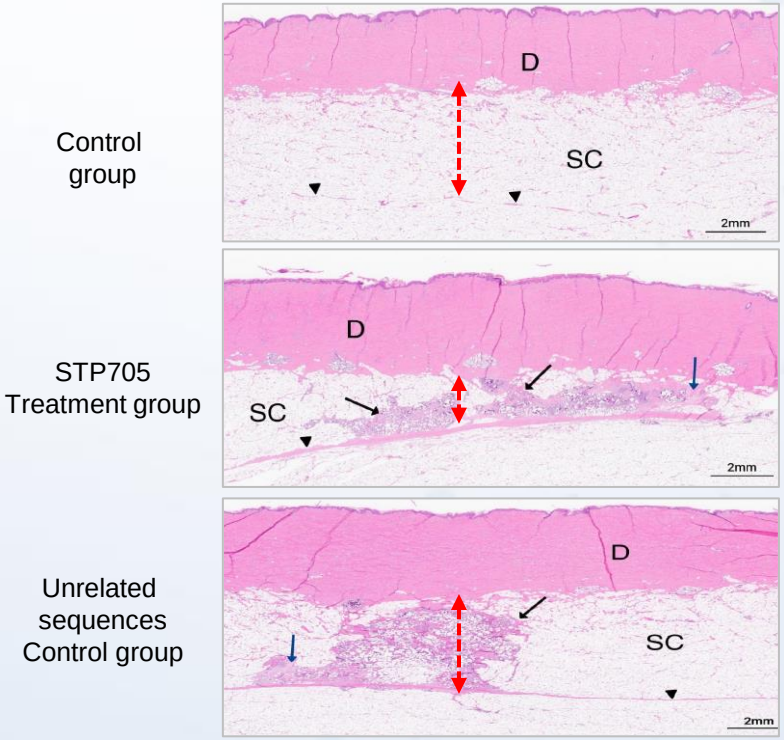
STP705 local treatment shows better treatment results and safety (on animal)

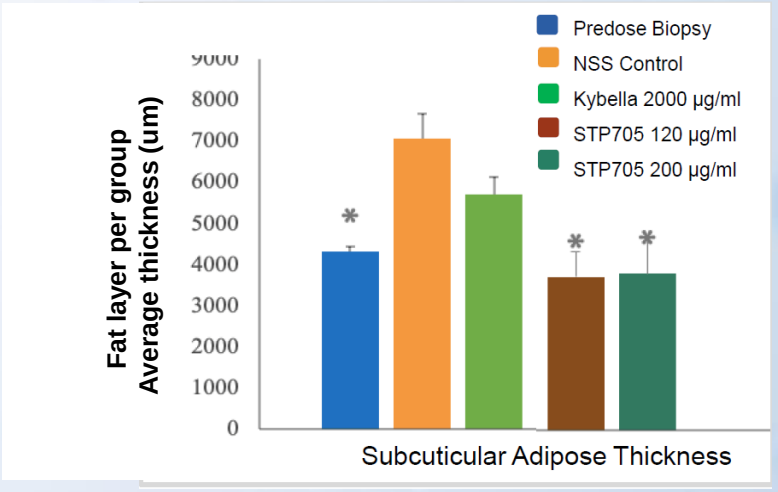
STP705 - Fat Remodeling Phase I

Accidental discovery of subcutaneous fat reduction in the treatment of isSCC

Preclinical: Minipig Model Efficacy Validation

STP705 1 dose, Kybella 2 doses, after 56 days

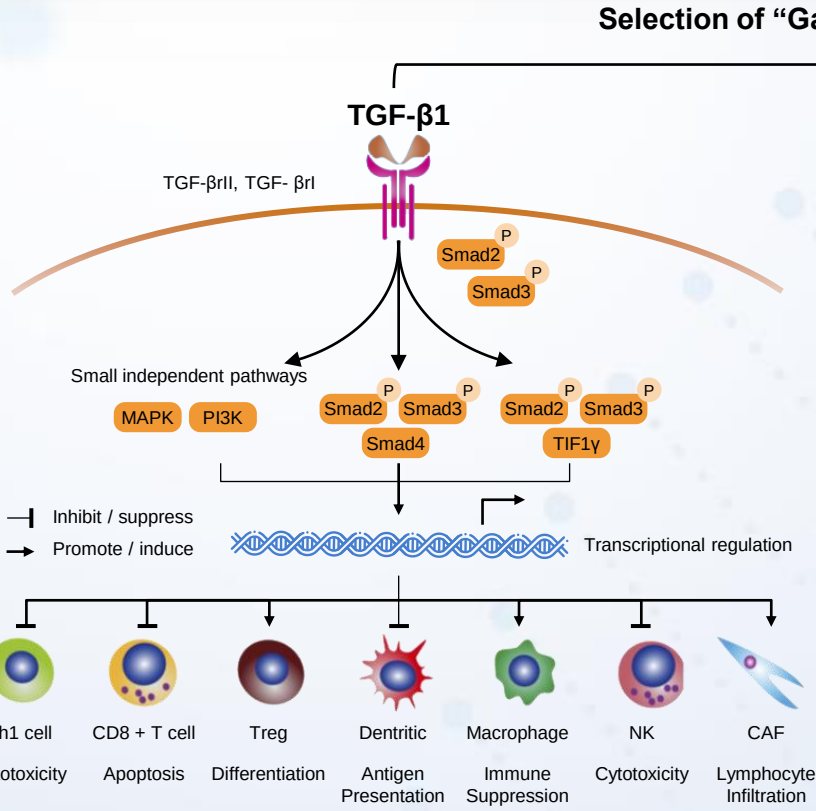




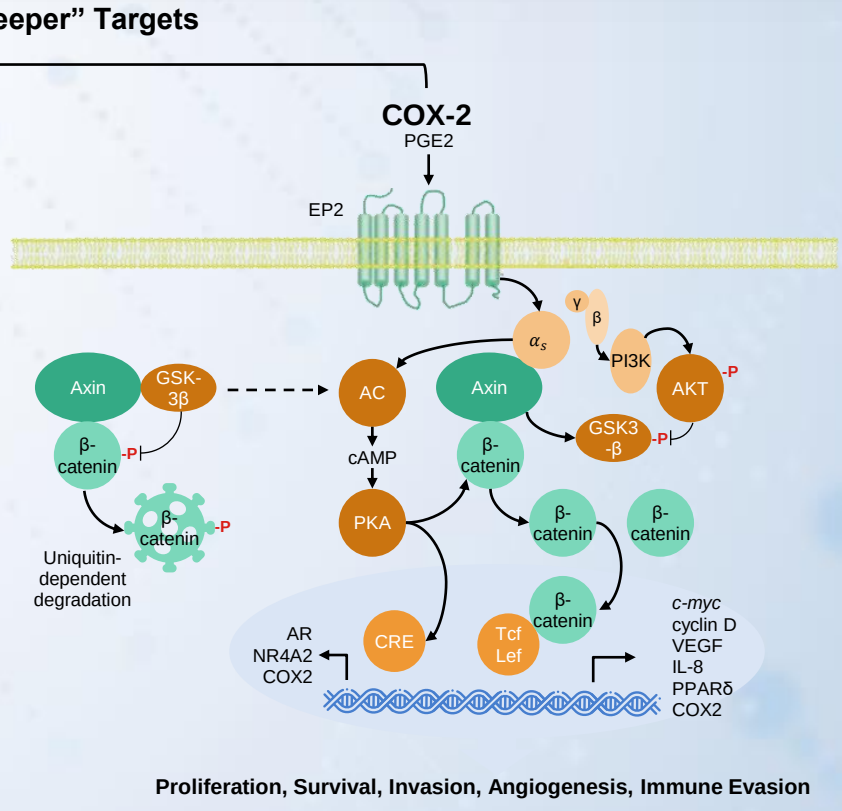
STP705 local treatment shows better treatment results and safety (on animal)

Innovative Dual-Targeted RNAi Therapeutics

Targeting both TGF-ß1 and COX-2



Source: *Bai, X., et al. OncoTargets and Therapy, 2019: 12, 9527–9538.*



Source: *Hashemi Goradel N, et al. J Cell Physiol. 2019: 234, 5683-5699.*

Mechanism of Action: The mechanism of action for both **TGF-β1** and **COX-2** in tumor biology and fibrotic disease is widely recognized

Drugability: A dual-targeted RNAi drug design inhibits both **TGF-β1** and **COX-2** simultaneously for high therapeutic potency

Minimize Toxicity: PNP delivery platform enables to create cell- and tissue-selective targeting of the TGF ß1/COX 2 inhibitory activity provided by the siRNA therapeutic and **avoiding whole body exposure**

Drug Formulations: Local formulation **STP705** uses **HKP**, and systemic formulation **STP707** uses **HKP+H**

Key Publication: Simultaneous silencing of TGF-β1 and COX-2 reduces human skin hypertrophic scar through activation of fibroblast apoptosis, *Lu, Li et al.* **Oncotarget**, 2017 (9)

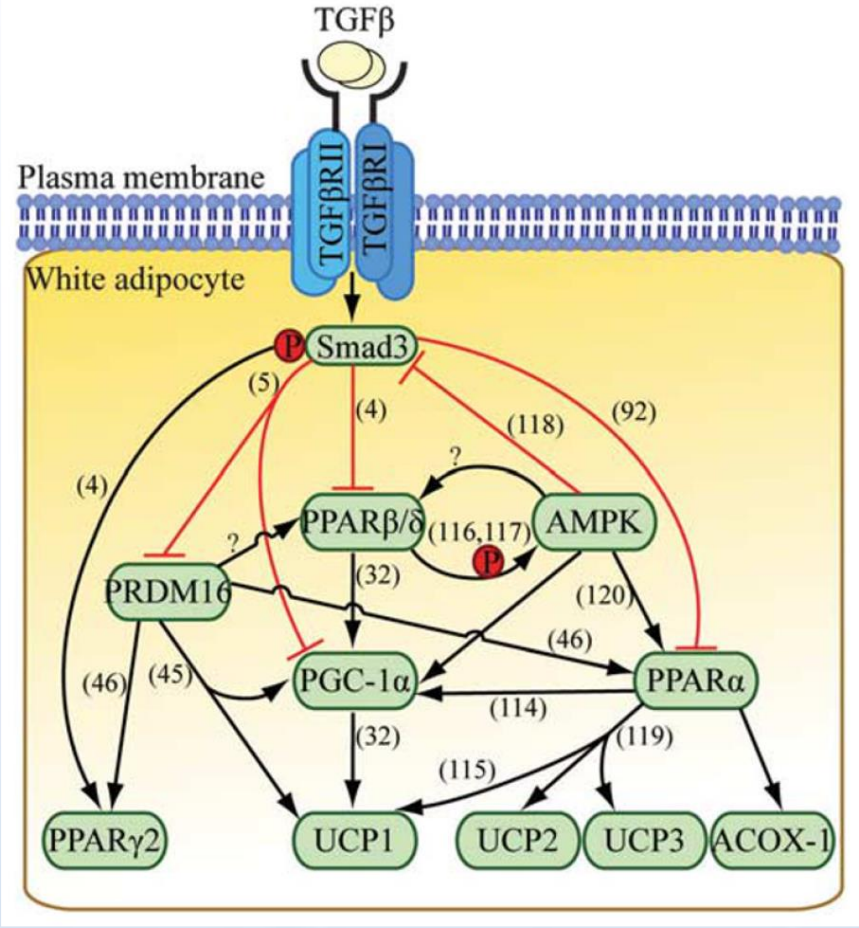
IP Protection for this Key Asset: Strong intellectual property position

STP705 Fat Remodeling - Mechanism of Action

TGFβ1 association with obesity

Recent findings on the role of TGFβ1/Smad3 signaling in the pathogenesis of obesity and type 2 diabetes have underscored its importance in metabolism and adiposity. Indeed, elevated TGFβ1 has been previously reported in human adipose tissue during morbid obesity and diabetic neuropathy.

TGF-b/Smad3 signaling in obesity and diabetes CK Tan et al

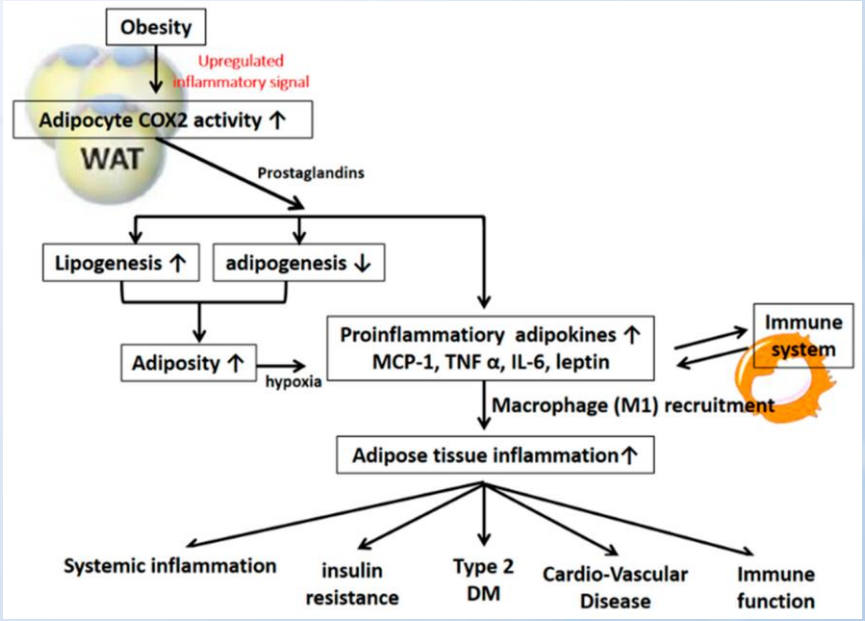


COX- 2 association with obesity

COX-2 is the key enzyme in eicosanoid metabolism that converts eicosanoids into a number of PGs, including PGD_2, PGE_2, $PGF_{2\alpha}$, and prostacyclin (PGI_2), all of which exert diverse hormone-like effects via autocrine or paracrine mechanisms. The COX-2 gene and immunoreactive proteins have been documented to be highly expressed and elevated in adipose tissue (AT) under morbid obesity conditions.

COX-2 activation in the epididymal AT is strongly correlated with the development of AT inflammation, insulin resistance, and fatty liver in high-fat-diet-induced obese rats.

Int. J. Mol. Sci. 2019, 20, 3115



STP705 Fat Remodeling - Protocol and Main Focus

STP705 fat remodeling clinical Phase I in progress

Clinical Protocol:

To evaluate the **safety and tolerability** of STP705, delivered via subcutaneous injection. STP705 will be administered to **6 subjects** on day 1, 28 and 56. Each subject will be treated with **7 injection points**. The dosing schedule is as follows:

- A cohort: STP705 120 µg, 0.5 ml and 1 ml (6 samples each)
- B cohort: STP705 240 µg, 0.5 ml and 1 ml (6 samples each)
- C cohort: STP705 320 µg, 0.5 ml and 1 ml (6 samples each)
- D cohort: Control Group (6 samples each)

Primary Endpoints:

To assess injection comfort, characterize **local and systemic safety**, and evaluate histological changes of subcutaneous doses of STP705, and to compare the safety and tolerability of three different concentrations of STP705 to select dosages for future studies

STP705 Fat Remodeling - Histological Scoring

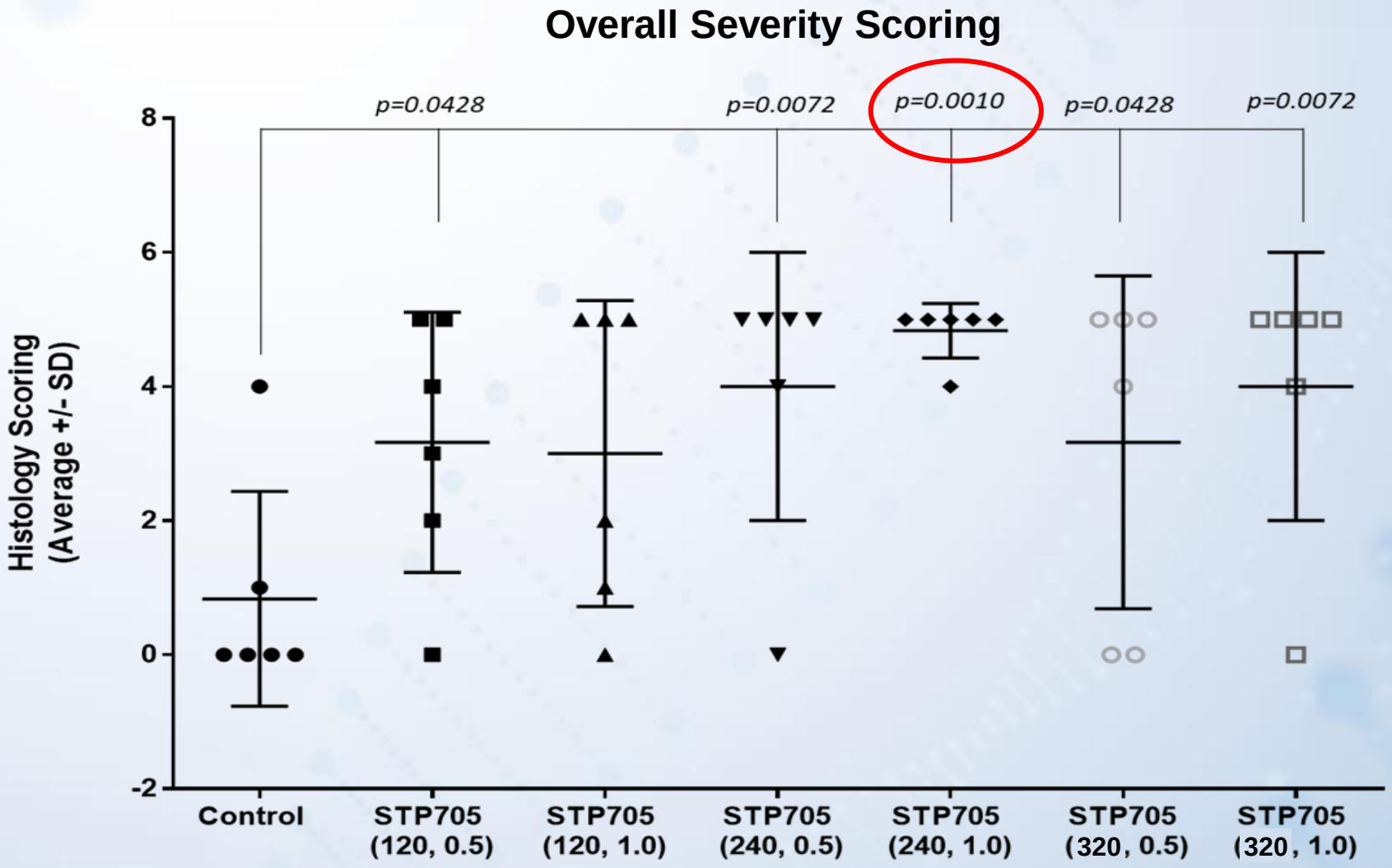
- **Study Design 7 Groups:**
  (i) placebo; (ii) 120ug (0.5mL injection), (iii) 120ug (1.0mL injection), (iv) 240ug (0.5mL injection), (v) 240ug (1.0mL injection), (vi) 320ug (0.5mL injection), (vii) 320ug (1.0mL injection)
- N= 6 subjects; each subject received treatments at different sites highlighted in the groups above
- Subjects were injected at 1st , 28th and 56th day up to 3 times

Histological Scoring	
No change	0
Mild inflammation/mild fibrosis	1
Lymphocytic infiltrate + hemorrhage	2
Panniculitis + fibrosis	3
Panniculitis with lymphocyte	4
Panniculitis + fat necrosis	5

- Statistical analysis was performed with non-parametric one-way ANOVA using Kruskal-Wallis test and Dunn's multiple comparison test

Data represents draft analysis using the interim analysis table.
Full evaluation by a clinical/biostatistician expert needs to be conducted to verify these results.

Adipose Tissue Comparison



Data represents draft analysis using the interim analysis table.
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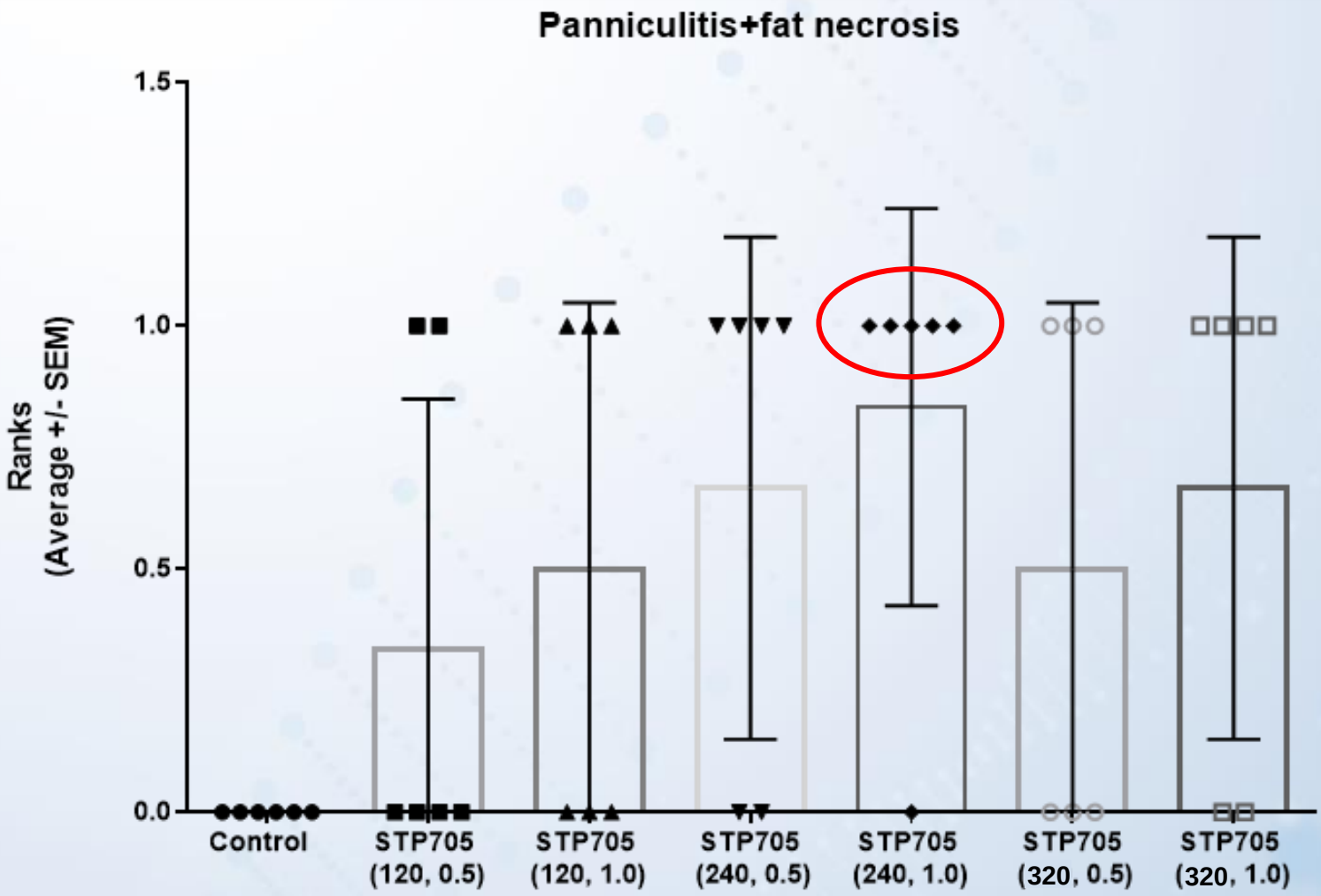
Treatment vs Control Groups (Changes in Fat Layer)



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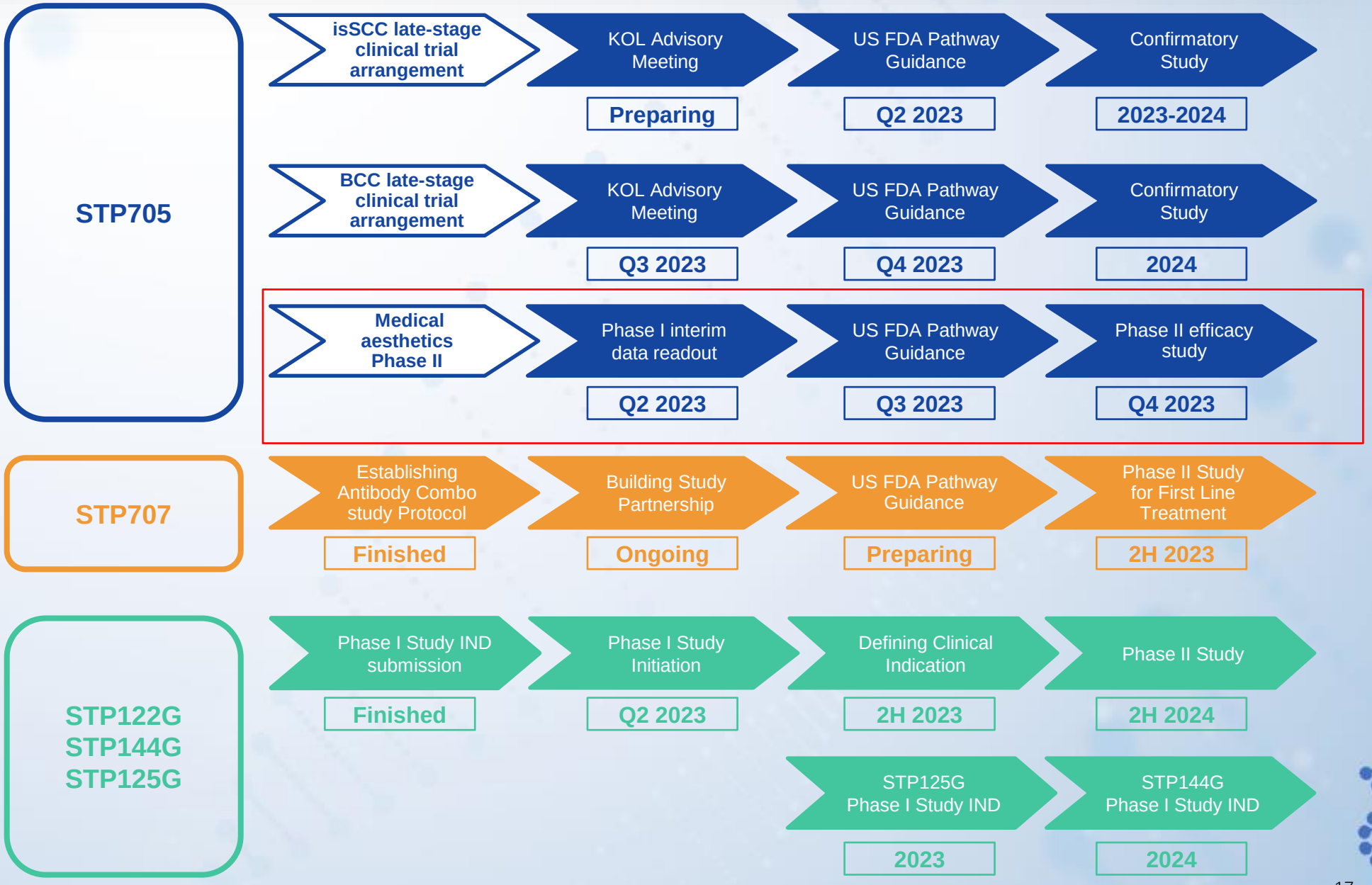
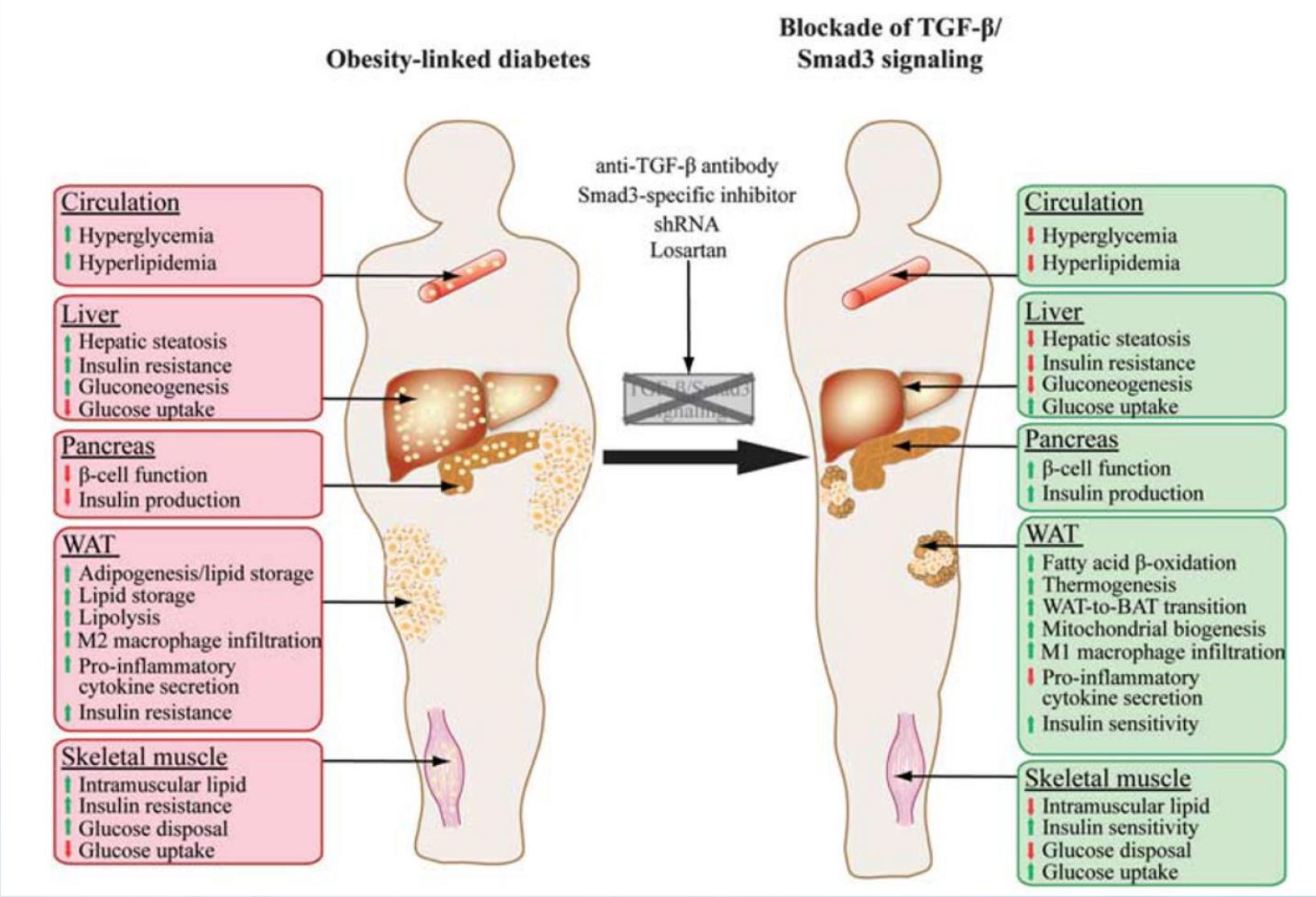
Full evaluation by a clinical/biostatistician expert needs to be conducted to verify these results.

Full Speed Ahead - Future Milestones



STP705/STP707 - Fat Reduction Mechanism of Action



RNAi - Great Potential in Fat Remolding Area

01 Enhance and apply our proprietary delivery platforms to advance the development of innovative therapeutic modalities for the treatment of a broad range of disease states and strengthen our intellectual property position

02 Rapidly advance development of our lead product STP705, STP707, and STP122G toward market approvals in a broad range of indications in the U.S. and Asia

03 Develop and commercialize a diverse portfolio of transformative RNA products in a broad range of therapeutic areas with significant unmet needs

04 Build a fully integrated biopharmaceutical company by advancing our capabilities in product development, expanding our internal GMP manufacturing capabilities, and developing commercialization abilities

05 Selectively pursue synergistic collaboration opportunities to maximize the potential of our clinical product candidates