

Tunable Delivery of Parathyroid Hormone with the Shielded Living Therapeutics™ Platform Provides a New Modality for Treatment of Hypoparathyroidism

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Introduction

- **Hypoparathyroidism** (low or minimal parathyroid hormone [PTH] production) is a rare endocrine disorder with an estimated 60,000 -115,000 patients diagnosed with chronic hypoparathyroidism in the US each year
- The most common cause of chronic hypoparathyroidism is surgical damage or removal of the parathyroid glands
- PTH is a **critical hormone for regulating calcium homeostasis** and its normal **plasma levels are tightly maintained** in the range of 10-60 pg/mL
- While replacement therapy with synthetic PTH hormone is a currently approved option for the treatment of hypoparathyroidism, a **key challenge is maintaining therapeutic levels within the physiological range**
- **SLTx** is a novel allogeneic cell-based platform which **enables tunable & long-term delivery** of Parathyroid Hormone

Shielded Living Therapeutics™ Platform

- This **non-viral, cell-based, modular platform** was designed to address two major challenges of allogeneic cell therapy:

Cell-to-cell interaction and rejection



Physical shield (2-compartment, modified alginate sphere)

Pericapsular fibrotic overgrowth (PFO)



Small-molecule conjugated alginate in outer layer



No PFO observed after 180 days

Empty spheres were administered to the non-human primates intraperitoneally via laparoscopic procedure.

Sustained and Tunable Delivery of PTH

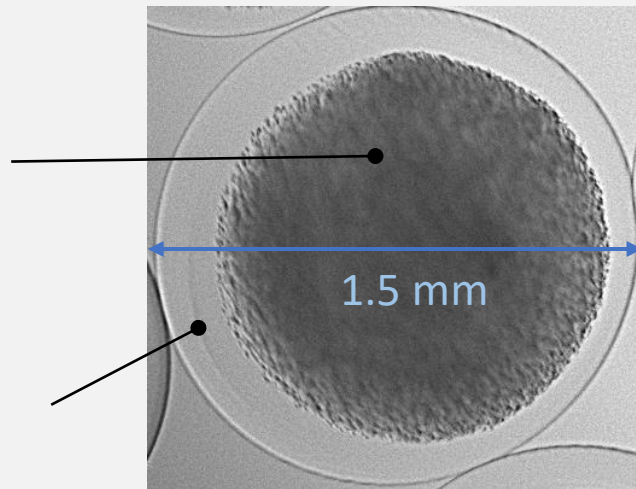
- We hypothesized that this platform can be used to deliver sustained and tunable delivery of human PTH

Inner Compartment:

- genetically modified human cells with tunable expression of PTH
- modified alginate designed to optimize cell function

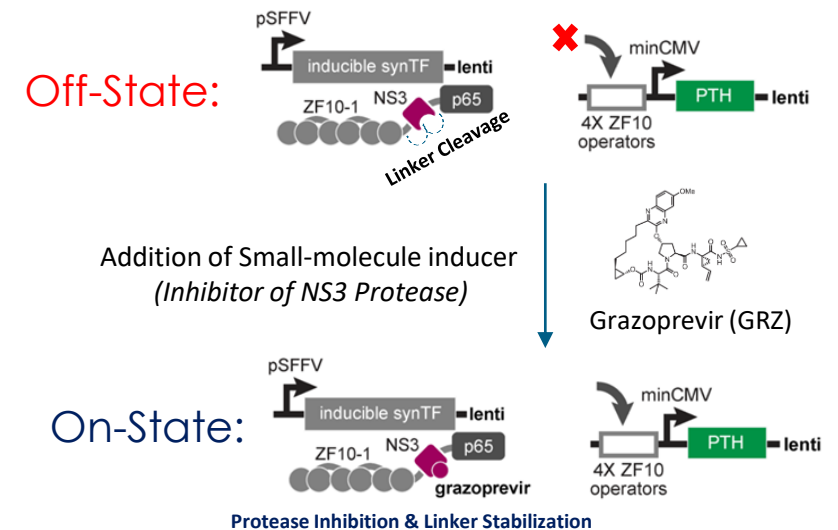
Outer Layer:

- modified alginate chemically linked to small molecule to minimize PFO



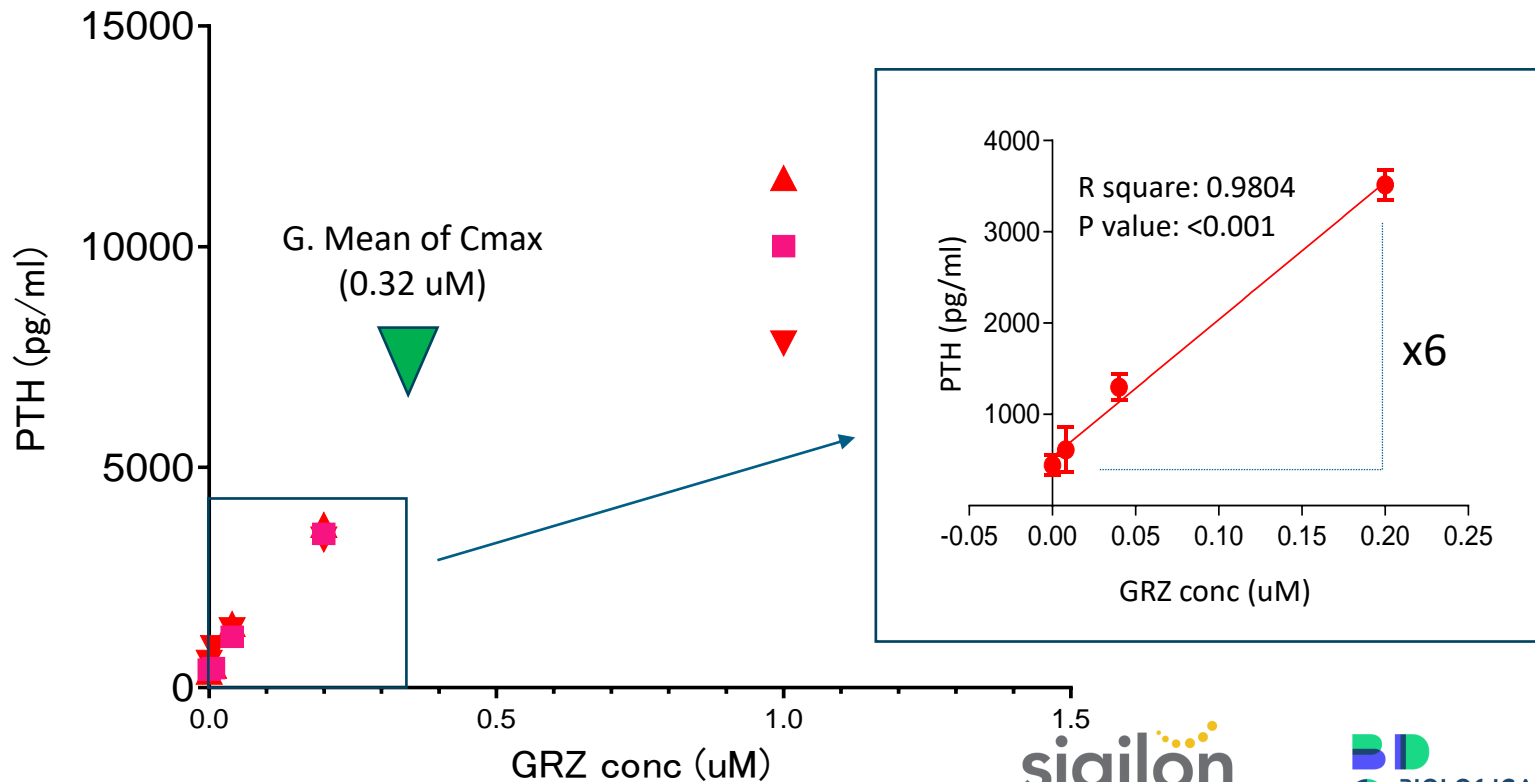
Bright field microscope image of a typical sphere

Design of a synthetic circuit to regulate PTH production using an oral drug



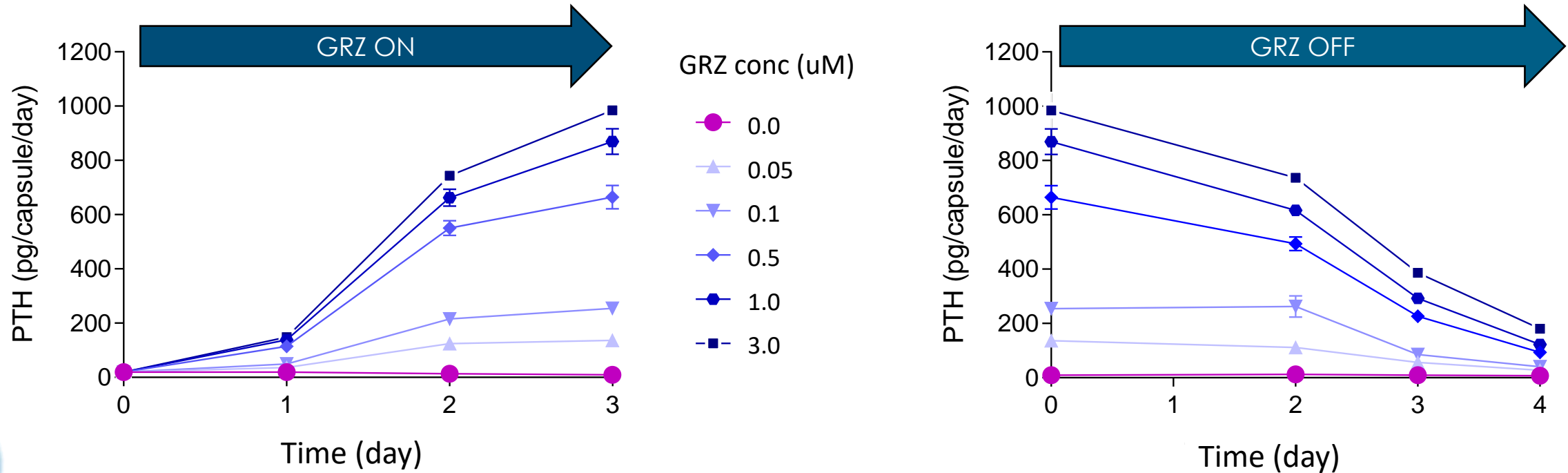
NS3-based Synthetic Circuit Enables Tunable Expression of PTH production from Engineered Cells

GRZ-responsive promoter



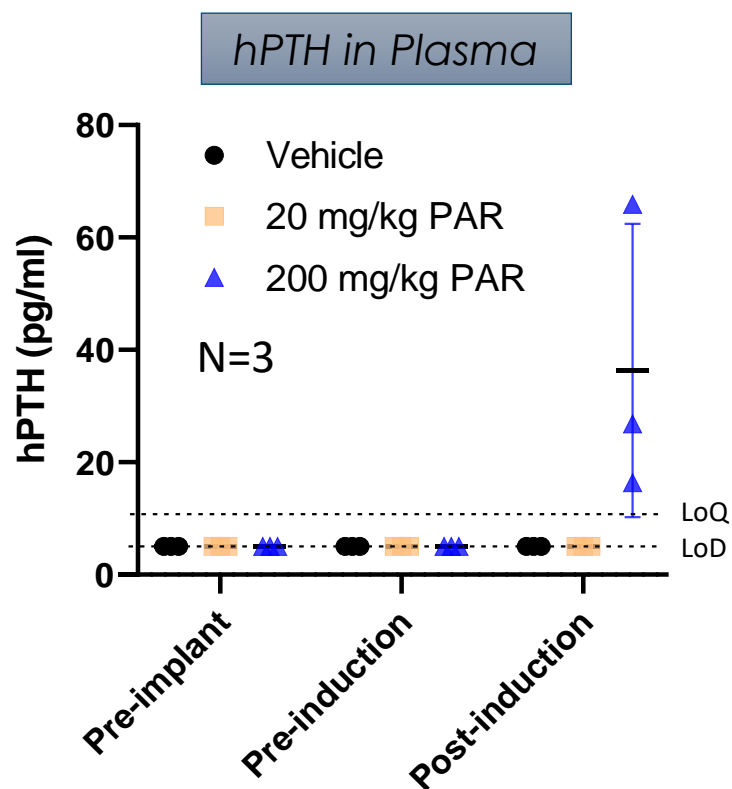
Tunable PTH expression obtained with GRZ concentrations amenable to oral dosing in humans

PTH Production by Encapsulated Cells



GRZ can titrate the PTH expression in encapsulated cells

SLTx Platform Enables Inducible PTH Expression *in vivo*



- Study Design: Nude mice were implanted with SLTx-spheres containing cells engineered with Tunable expression of PTH
- NS3 inhibitor (inducer): Paritaprevir (PAR)
- Inducer-dosing: 20 or 200 mg/kg of Paritaprevir for 4 consecutive days via oral gavage
- PTH detection: After the 4-day induction bioactive hPTH levels in plasma were determined by PTH (1-84) ELISA.

Conclusions

- **PTH production** was **efficiently induced** from cells engineered with a circuit in a **dose-regulatable manner**
- Reciprocally, withdrawal of the inducer led to **complete attenuation of PTH production**
- Dose-responsive PTH production was **maintained after encapsulation** of engineered cells into the two-compartment alginate spheres
- Finally, we demonstrated the functionality of the encapsulated cells *in vivo* with **induction of human PTH at physiological levels in recipient animals** by oral administration of the small-molecule inducer
- Collectively, our data demonstrate **a novel modality utilizing an innovative cell-based platform** for the treatment of hypoparathyroidism which provides **durable and tunable replacement of PTH**, potentially overcoming limitations associated with current therapies

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