

EverShield

Long-acting, biodegradable implants for local, sustained drug release

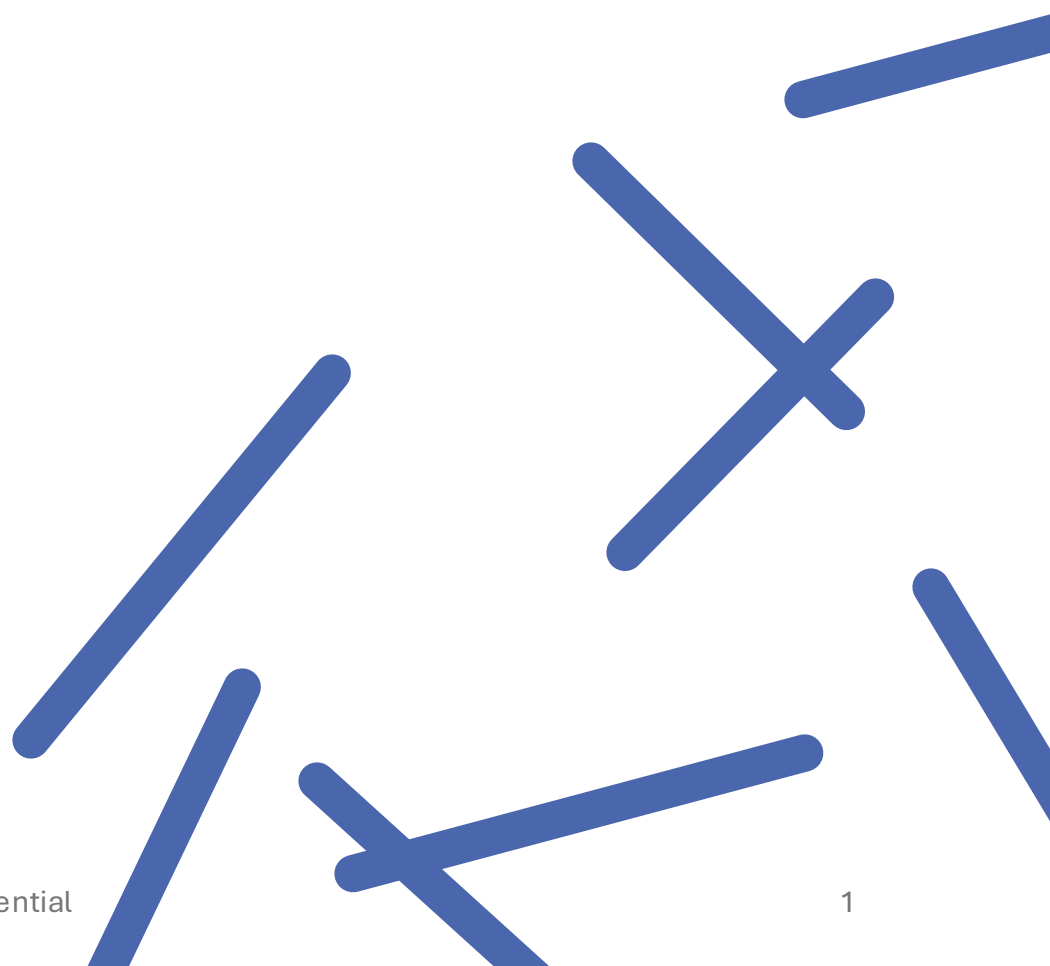
Mark Saltzman, PhD | Blavatnik Application | Fall 2024

ROBERTS

INNOVATION FUND

Women's Health Research at Yale

Yale ENGINEERING



The right founding team



Hugh Taylor, MD

Chair, OB/GYN & Reprod. Sciences
Yale New Haven Hospital

Leader in endometriosis research and treatment



Mark Saltzman, PhD

Goizueta Foundation Professor
Yale School of Biomedical Engineering

Leader in nanoparticle engineering and novel drug delivery systems

YALE VENTURES

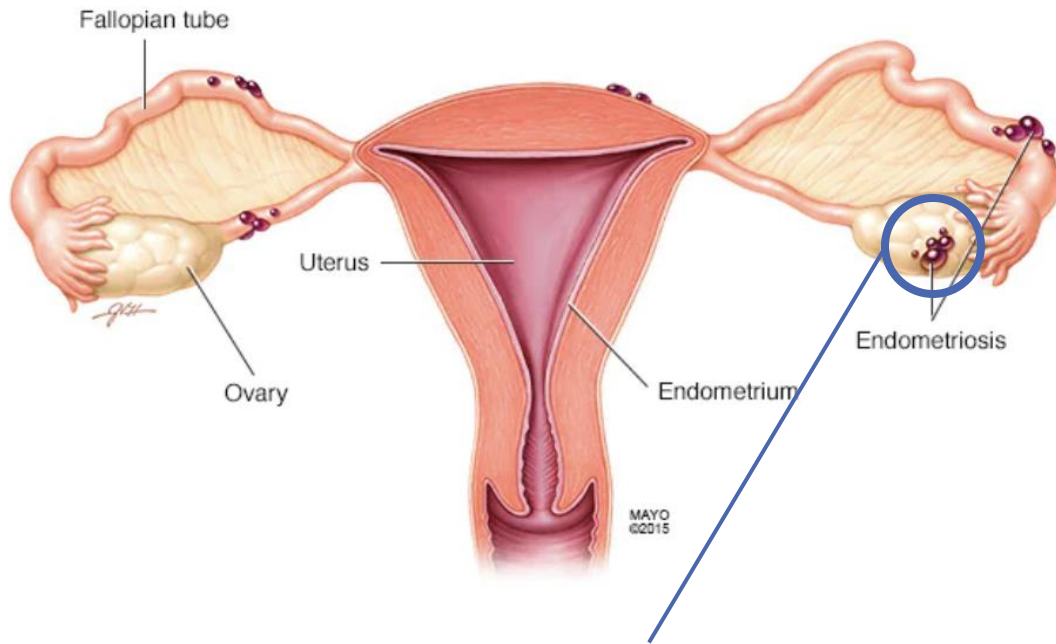
Shannon Anderson, PhD, Business Development

Robert Williams, PhD, Blavatnik Fellow

Urgent unmet need: non-invasive, local endometriosis treatment

10-15% of women experience endometriosis during reproductive ages:

190M women worldwide; 6.5M in US



characterized by peritoneal endometriotic lesions

Debilitating symptoms

- Infertility (60%)
- Debilitating chronic pain (80%)
- GI/Urinary Symptoms

Inadequate Standard of Care

1. **Progestins** – 1/3 patients fail; significant side effects
2. **Surgical excision of lesions** – recurrence within 2 years
3. **GnRH modulators** – avoided due to side effects
4. **AR Modulators** - systemic side effects
5. **Hysterectomy** - infertility

Significant Societal Impact

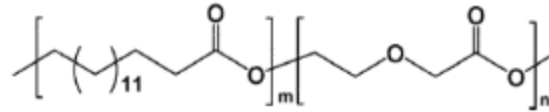
- Patients experience financial hardship
- Avg 11 hours/week of work productivity loss
- \$119B US economic burden

Current treatments have systemic side effects, stressing the need for local drug delivery

Overview of Hormonal Treatments for Endometriosis		
<p><u>1.</u></p> <p>GnRH Modulators</p> <ul style="list-style-type: none">• <i>Side Effects:</i> Hot flashes and bone thinning, where long-term usage may lead to osteoporosis• Local delivery not possible due to only working in the pituitary	<p><u>2.</u></p> <p>Progestins</p> <ul style="list-style-type: none">• <i>Side Effects:</i> Mood disorders, bloating, breast tenderness• 1/3 patients fail due to progestin resistance <p><u>Our Opportunity</u> Can avoid systemic side effects and overcome resistance if administered locally</p>	<p><u>3.</u></p> <p>Danazol</p> <ul style="list-style-type: none">• <i>Side Effects:</i> Acne, oily skin, male-patterned facial hair growth, weight gain• High success rate• Unpopular and outdated compared to current treatments

EverShield: committed to protection over the long term

We have developed a novel **implantable technology** that enables the long-acting, local release of APIs



Poly(ω -pentadecalactone-co-p-dioxanone) or PDL-co-DO

Tunable to control release rates and duration¹

Safe PDL-co-DO polymer will degrade into non-toxic metabolites²

Biodegradable and stable for long durations

Compatible with a range of APIs

Validated in multiple disease-relevant *in vivo* models

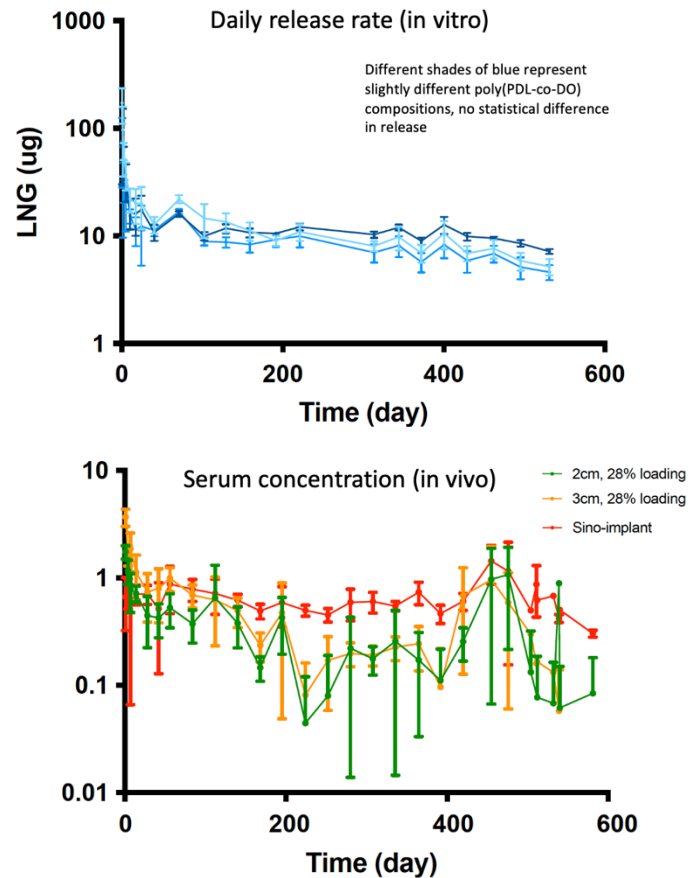
Scalable manufacturing process

1. Issued **patent U.S. 11,766,400** covering use of this polymer for long-acting implants, with elements of design to control release rate and duration
2. Predicted safety based on known safety of monomers and metabolites. Confirmed by independent report by **Integrated Nonclinical Development Solutions, Ann Arbor, MI.**

EverShield implants are **biodegradable, durable, and mechanically strong**

Long-acting

Levonorgestrel (LNG) release is sustained over time, with good *in vitro*: *in vivo* correlation

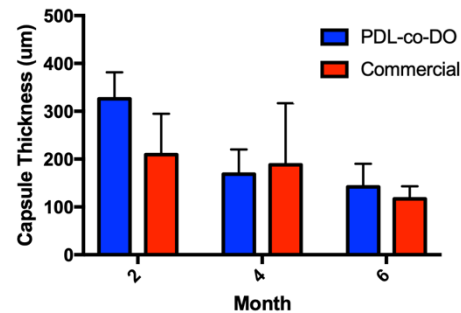
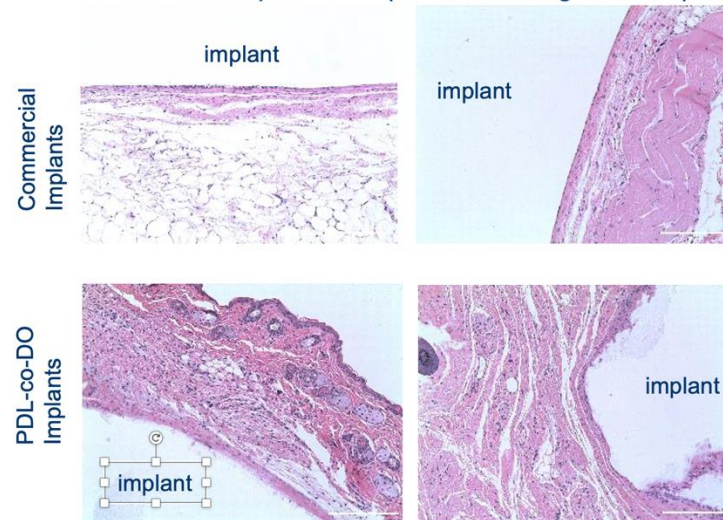


LNG is chemically stable over the multi-year release at 37°C

Well-tolerated

Poly(PDL-co-DO) is as inert on implantation as other FDA-approved implant materials

2 Months after Implantation (H&E, 20× Magnification)



Mechanically Strong

Withstands > 5 months of dissolution at 50 °C

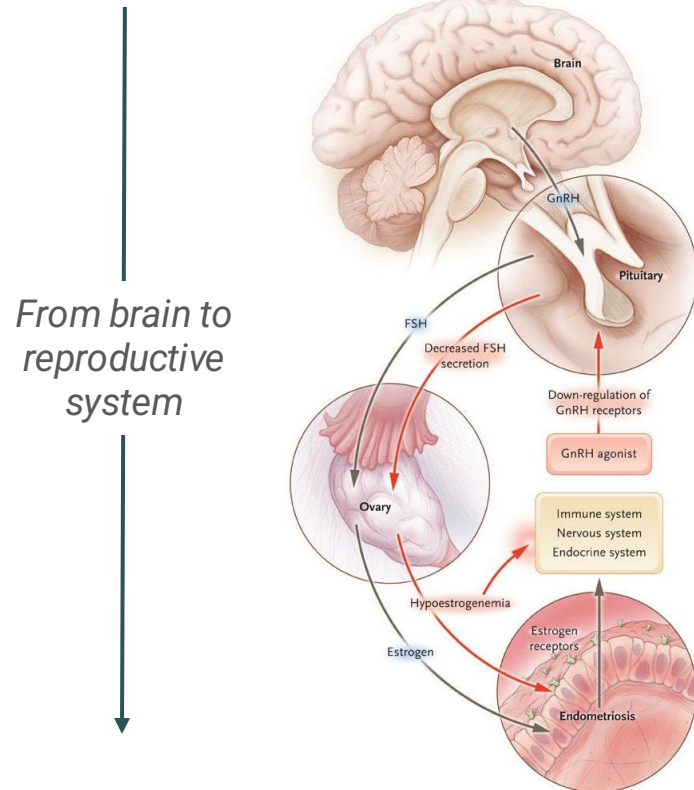


Comparable to 18 months at 37°C

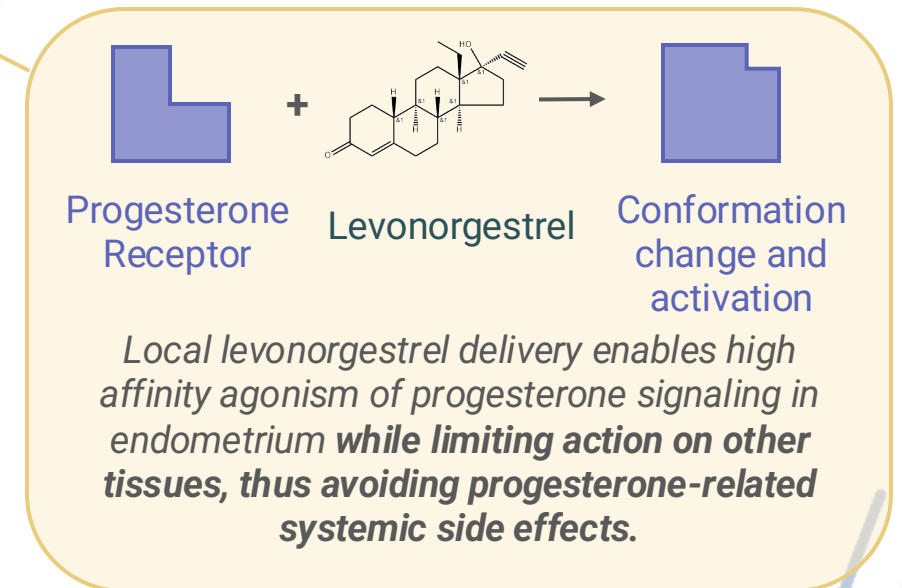
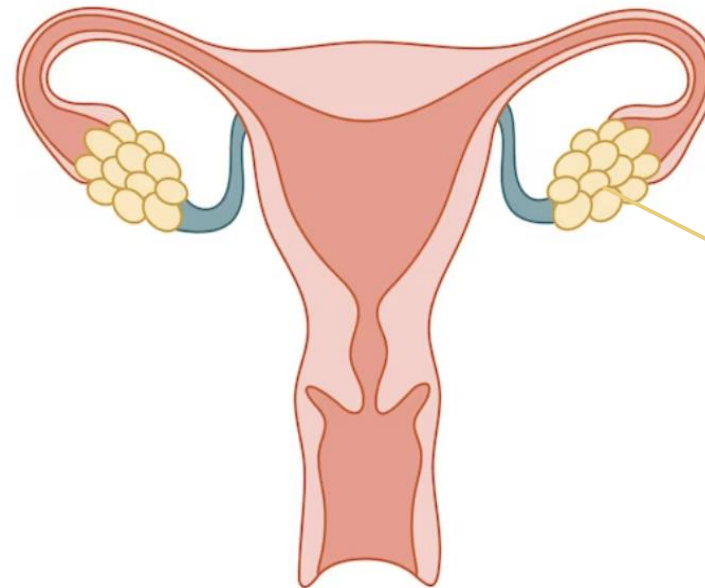
Solution: Sustained, local release of the FDA-approved progestin Levonorgestrel

High local doses of Levonorgestrel is a potential disease modifying treatment

Systemic Drug Administration Affects Multiple Tissues



Localized Mechanism



Competitive analysis for endometriosis treatments

		Route of Administration	Frequency	Average Retail Price/Year*
	EverShield	Intraperitoneal	1x every 2-3 years	\$1.2k
GnRH Modulators	Zoladex (goserelin implant)	Subcutaneous	1x every month	\$12k
	Lupron Depot (leuprolide acetate for depot suspension)	Intramuscular	1x every month	\$21.6k
	Orilissa elagolix tablets <small>150mg 200mg</small>	Oral	1x daily	\$14.4k
	Synarel (nafarelin acetate) nasal solution	Nasal	2x daily	\$38.3k
Progestin	depo-subQ provera 104* <small>(medroxyprogesterone acetate) injectable suspension (104 mg/0.65 mL for subcutaneous use)</small>	Subcutaneous	1x every 3 months	\$195
	Mirena 20 micrograms/24 hours intrauterine delivery system	Intrauterine device**	1x every 5-8 years	\$150-\$240 not including insertion/de-insertion costs
Combo	Myfembree (relugolix, estradiol, and norethindrone acetate) tablets 40 mg, 1 mg, 0.5 mg	Oral	1x daily	\$14.9k








EverShield will offer a long-acting, biodegradable treatment for endometriosis at a price comparable to existing solutions

*Referring to lowest dosage and normalizing dosage frequency to a year

**Must be physically removed after 5-8 years

Evershield's competitive advantage

Current degradable implants **don't last long enough**, and non-degradable implants **require removal**

Durability	Non-degradable, Long-acting (> 1 year)	 Norplant – Contraception  Jadelle – Contraception  Yutiq – Uveitis	<div style="border: 2px solid orange; border-radius: 15px; padding: 10px; background-color: #fff9c4;"> <p style="margin: 0;">EverShield</p> <ul style="list-style-type: none"> ✓ Long-acting ✓ Biodegradable </div>
	Non-degradable, medium-acting (1-6 month)	 Estring – Menopausal symptoms  Nuvaring – Contraception  LIRIS – Cystitis  Medtronic SINUVA – Nasal polyps	
		Degradability	

EverShield implants can address unmet needs for a wide range of conditions

Sustained, local release of FDA-approved drugs can improve efficacy, patient compliance, and side effect profiles

Women's Health

Endometriosis

Bazedoxifene

Danazol

Levonorgestrel

Chronic Pain

Arthritis

Dexamethasone

Anti-retrovirals

HIV

Dolutegravir

Hormone Replacement

Hypothyroidism

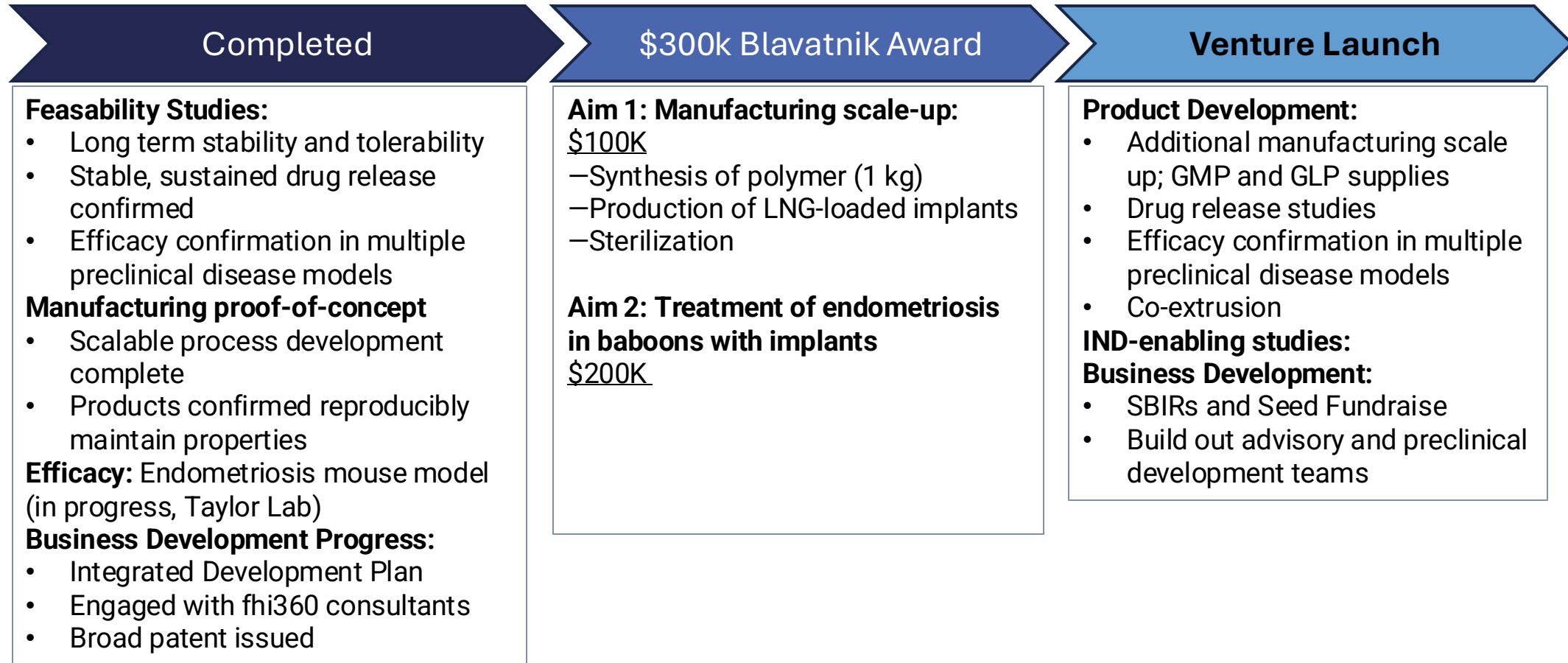
Synthroids

Cancer

*Intratumoral
Chemotherapies*



Current progress and launch plan



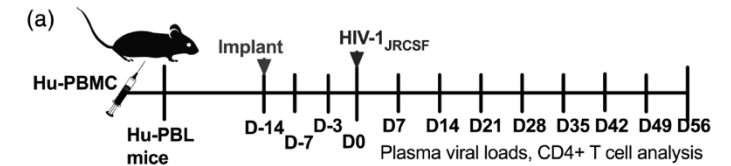
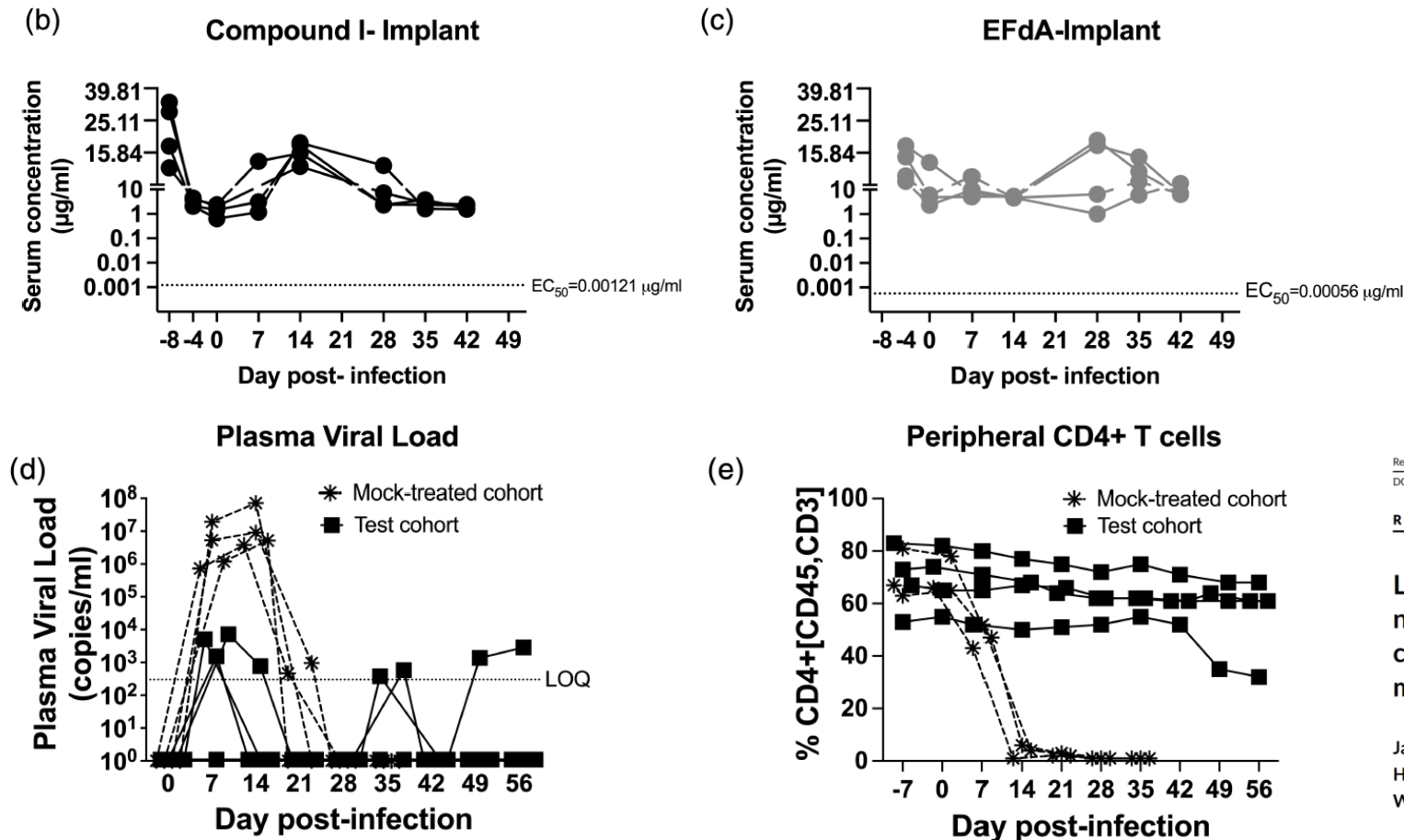
Supplemental



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Preclinical Example 2

- Anti-retroviral agents are released from our implants over sustained periods with promising results in humanized mice



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RESEARCH ARTICLE

BIOENGINEERING &
TRANSLATIONAL MEDICINE

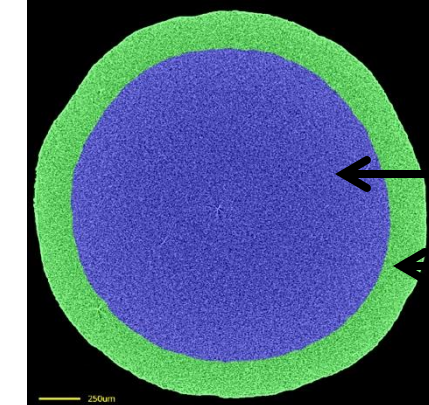
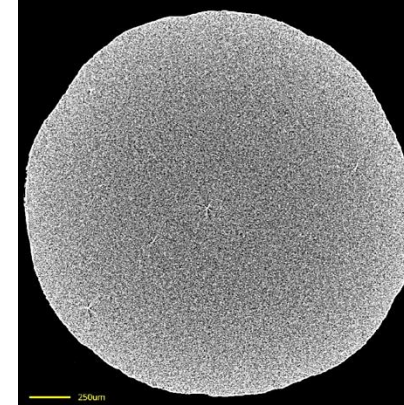
Long-acting and extended-release implant and nanoformulations with a synergistic antiretroviral two-drug combination controls HIV-1 infection in a humanized mouse model

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Demonstration of platform potential of the technology

EverShield implant has been optimized and produced at scale

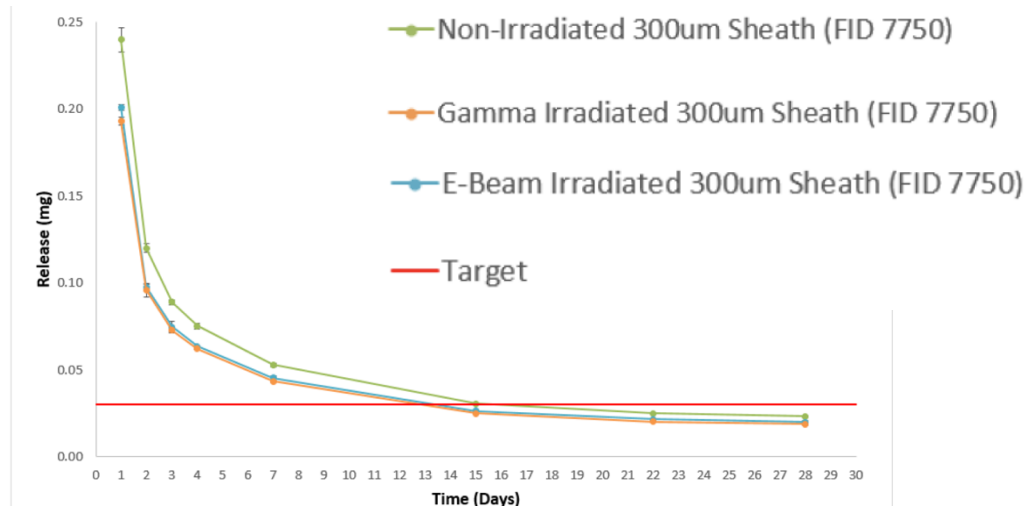
Confirmation of properties by advanced imaging (DigiM)



Core
Shell

Resolution = 2.82 μm

Confirmation of release characteristics from manufactured, sterilized implants



Control of release duration by core-sheath structure

