

Development of a Drug Delivery Surgical Staple

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Background

- Morbidity in surgery is directly related to technical factors.
- Improvements in technique, clinical care, and antibiotics have improved morbidity and mortality in surgery.
- New methods that combine accurate technical performance with site specific delivery of bioactive agents will improve these figures further.

Background cont'd

- The most rapid and reliable anastomotic technique is the surgical stapler.
- The staples provide accurate tissue apposition while evenly distributing tension, this is a major component of wound healing.
- Other elements in wound healing include adequate tissue oxygen delivery, freedom from infection, and adequate substrate for scar formation.

Stapler history

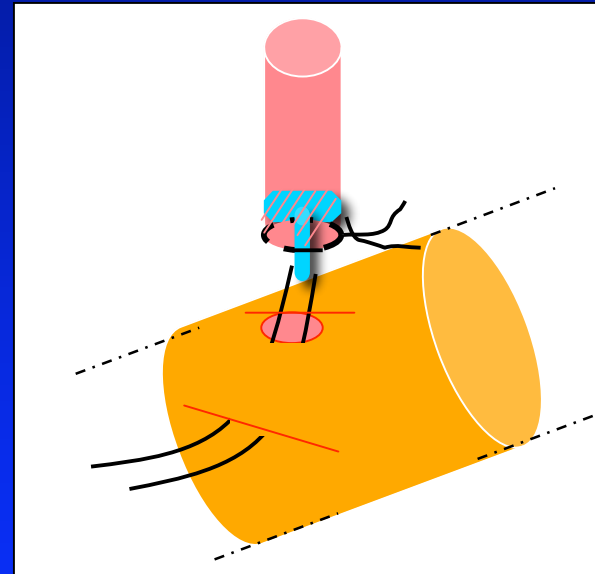
- Since its introduction to this country in the 1970s, the surgical stapler has not changed significantly:
 - The three formats: linear, linear cutting, and circular cutting have been modified for laparoscopic use, and various changes were made in ergonomics.
 - The staples remain steel or titanium of a standard size.
 - Absorbable staples exist, but are not widely used.



Mode of Employment



Stomach anastomosis



Bile duct anastomosis

Limitations of current surgical staplers

- No therapeutic component.
- They have not been miniaturized for use in organs with a small lumen.
- Scar formation within small lumen organs leads to obstruction.
- Non-absorbable staples may induce inflammation or stone formation and block a bile duct or ureter anastomosis.

Solution

- Development of a rapid and efficient anastomotic device for small lumen structures.
- Site specific delivery of a bioactive agent at the anastomotic site to improve the morbidity of the procedure.

Our unique and enabling features

- Allows delivery of a bioactive agent to the site where it is needed.
- May be used in any size or configuration using the polymer.
- The composition of the staple allows control of the timing of bioactive agent delivery.

Areas for Technology Transfer

Potential Applications

Surgery in:

- Bile duct
- Ureter
- Blood vessels
- Any site where conventional staplers are used, to improve morbidity/outcomes

Therapeutic Uses

Delivery of:

- Wound healing modulators
- Antibiotics
- Chemotherapeutic agents
- Radioactive, fluorescent, or contrast agents for imaging.
- Vaccines, immunotherapy
- Gene therapy

Benefits to Patient

- Shorten operative time and accuracy in small structures.
- Lower the rate of recurrent tumors.
- Lower the rate of infection or leak in an anastomosis.
- Improve outcomes of surgery overall.

Market Analysis

- Surgical staplers global sales \$890 million (1999)
- Circular stapler sales were \$400 million
- Projected wound closure market was \$1.76 billion in 2003
- Projected market of 60 to 120,000 procedures on bile duct benign/malignant combined
- laparoscopic info

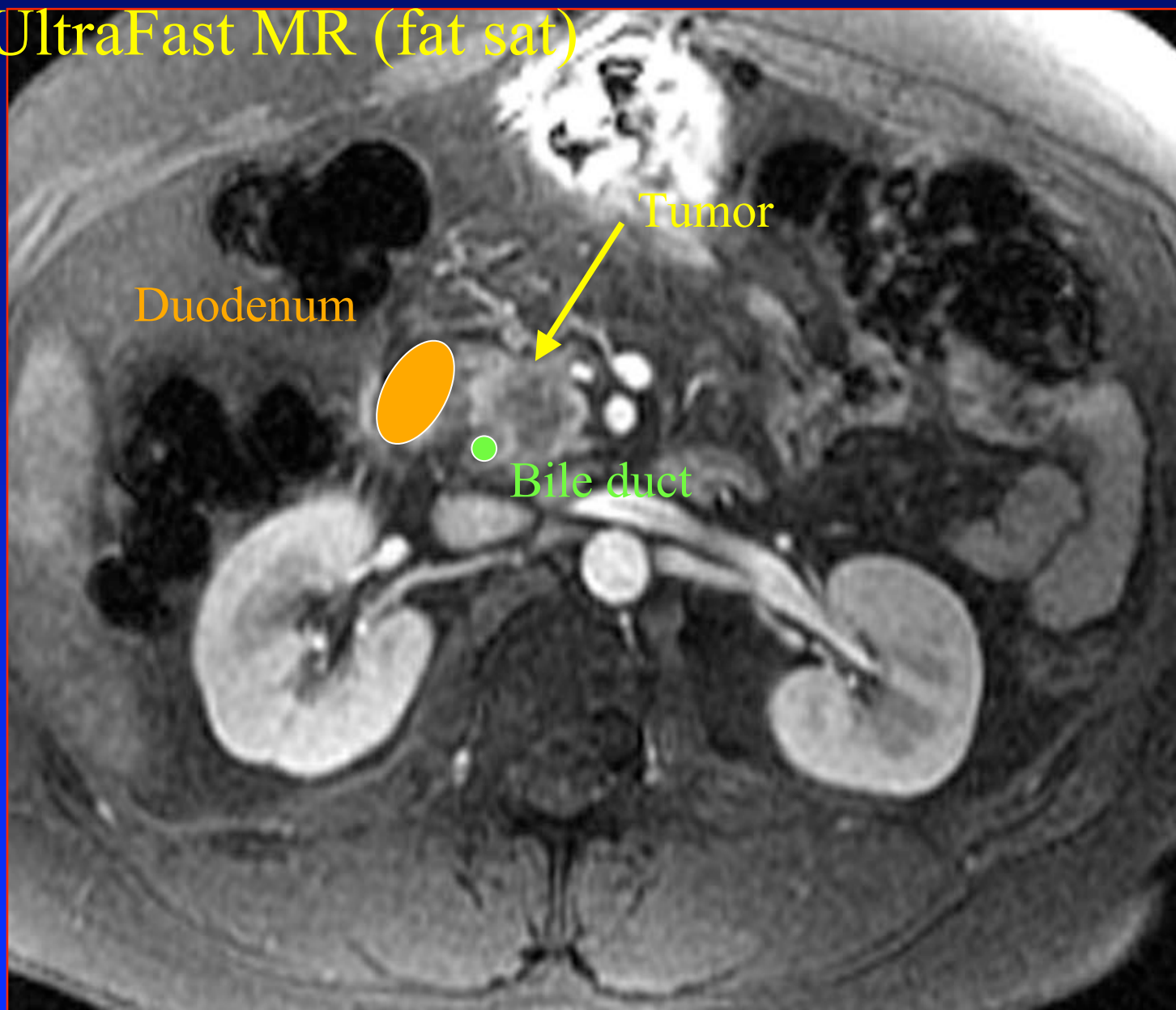
Pilot population : Bile duct surgery

- Pancreatic Cancer
 - 29,200 New Cases 2001
 - 10th most common site in men and women
 - 4th leading cause of cancer death
- Peri-ampullary cancer
 - Includes bile duct, ampulla and duodenum
 - Up to 10,000 additional cases
- Benign bile duct obstruction
 - Pancreatitis, inflammatory conditions
 - 18,000 procedures annually
- Liver transplant 5-7,000 cases annually

Why Choose Bile Duct Surgery for our clinical end point?

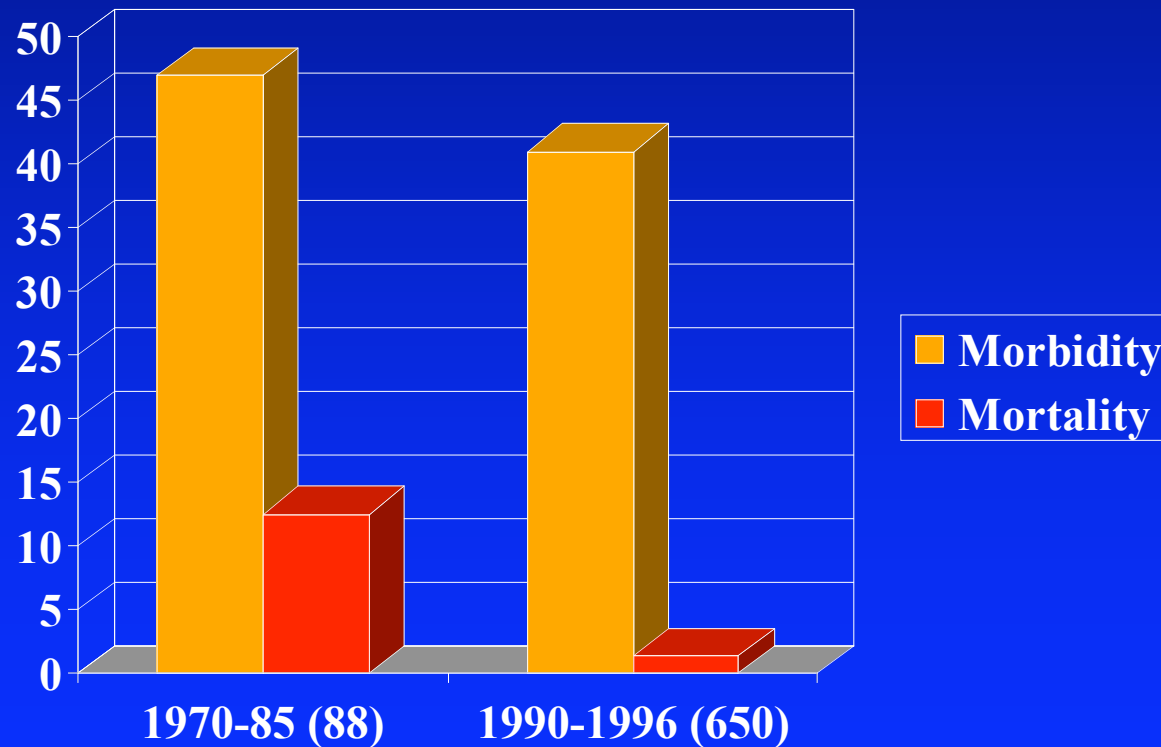
- 3 decades of data support the routine use of surgical staplers anywhere in the GI tract.
- Morbidity and mortality in GI surgery are acceptably low, although there is always room for improvement.
- Morbidity and mortality for procedures involving the bile duct remain unacceptably high.
- Laparoscopic/Endoscopic approaches to these areas are routine and a small device deployed through this route of access would be welcome.

UltraFast MR (fat sat)



Therapeutic Staple

Operative Morbidity and Mortality (Johns Hopkins) Pancreatic Surgery



1. Ann Surg 1987;206:358-365

2. Ann Surg 1997;226:248-260

Power Calculation

$$N = \frac{\{z_{\alpha} \sqrt{[2\Pi_1(1 - \Pi_1)]} - z_{\beta} \sqrt{[\Pi_1(1 - \Pi_1) + \Pi_2(1 - \Pi_2)]}\}}{(\Pi_1 - \Pi_2)}$$

z_{α} = Significance Level of < 0.05 , z score = 1.96

z_{β} = Power Level, - 1.645 at power 90 or -0.84 at power 80

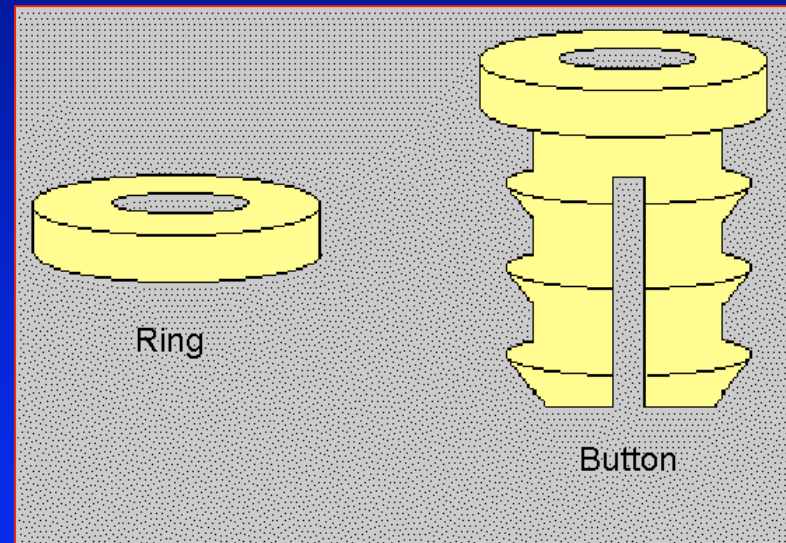
Π_1 = proportion one

Π_2 = proportion two

Study	Baseline	Difference	Power	N
Staple	45%	30% reduction	90%	45 per group
Mammograms	90%	5% improve	90%	450 per group

Our prototype

- We have developed the concept of the bile duct rivet or button fashioned from bioabsorbable polymer (PLA, PLGA)



Description

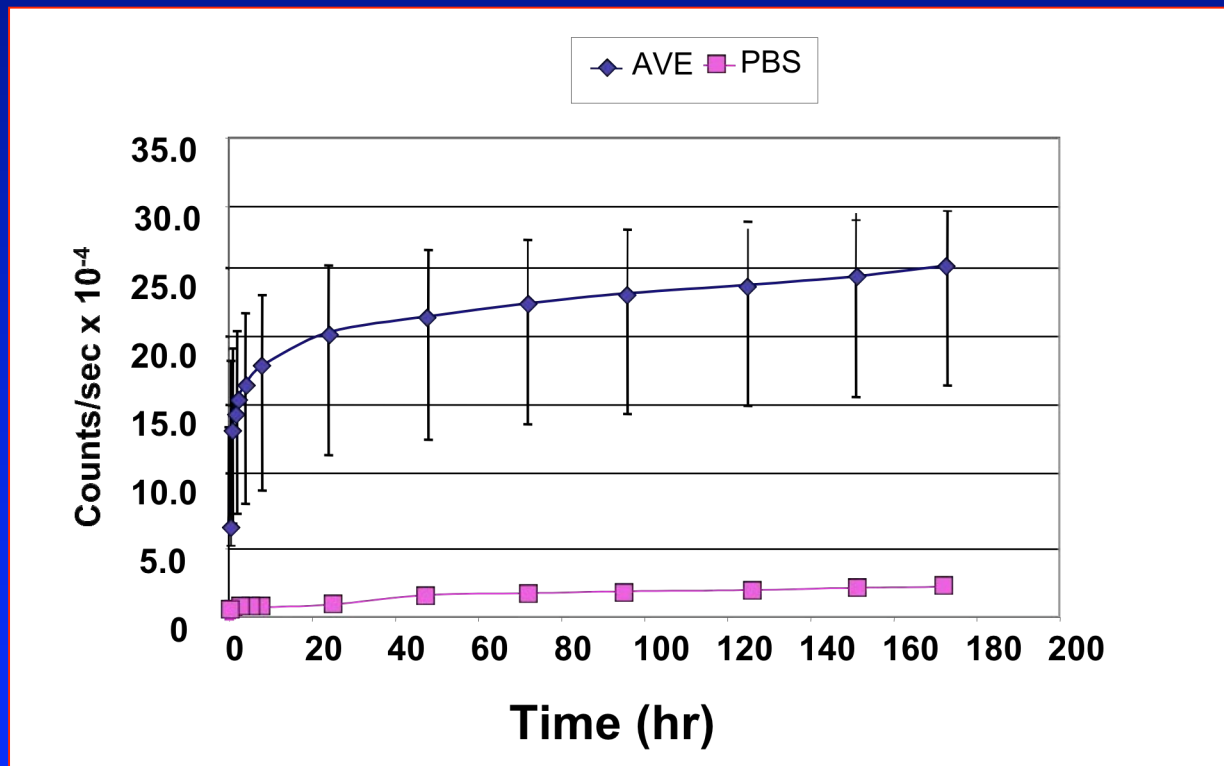
- The prototype ring portion of the ‘button’ was fashioned using solvent casting.
- The bioactive agent (fluorescent labeled protein) was incorporated during manufacture.
- Changing the ratio of monomer units in the backbone of the polymer will create different drug release profiles.



Drug Loading and Capacity

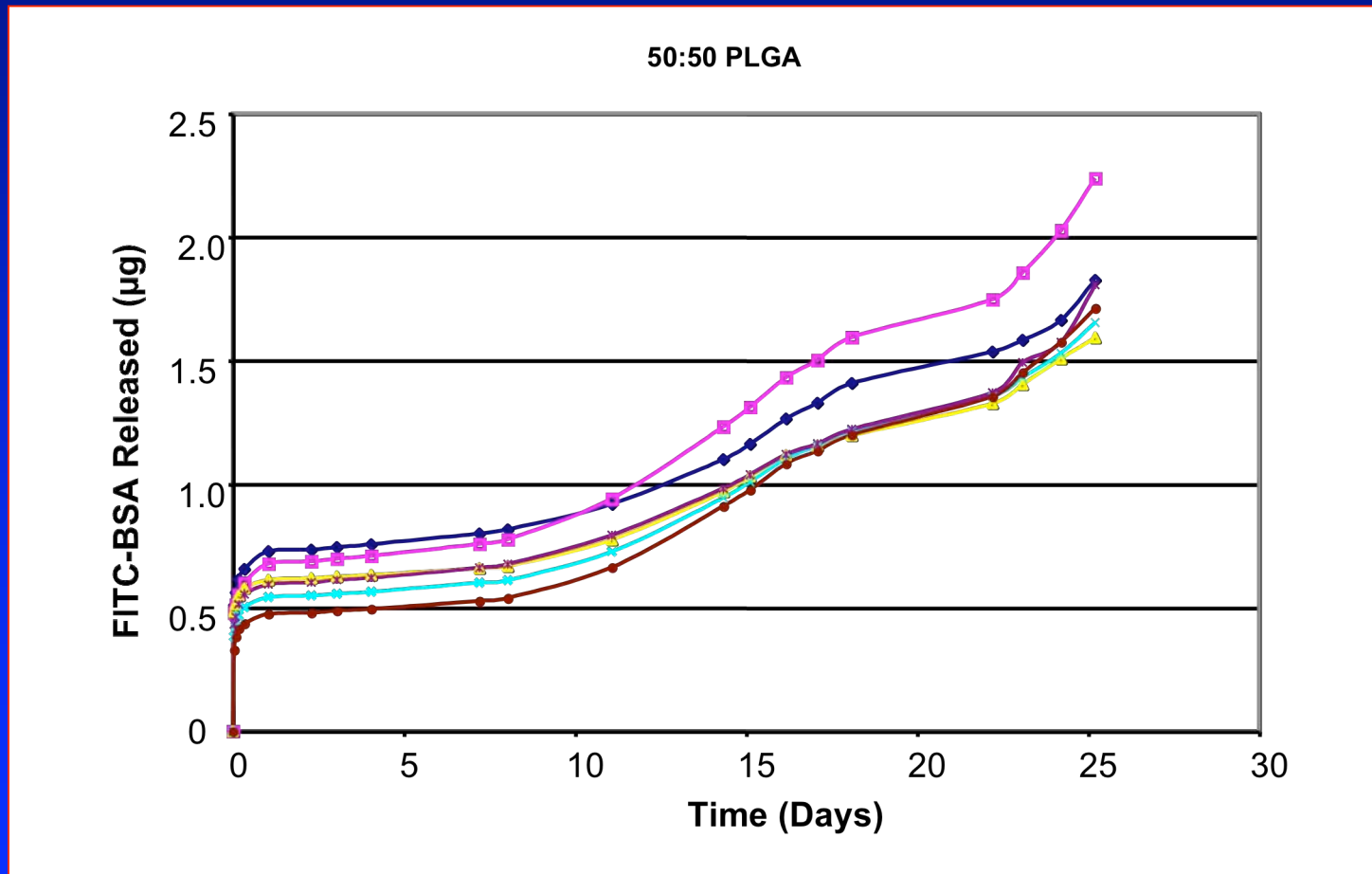
- Average ring ~ 0.1 g polymer
- Drug loadings from 1-50% by weight
- 10% represents ~ 10 mg protein
- Loss ~3%/day 0.3 mg/day
- It has been shown (1992) in pig that 5 μ g TGF- β sprinkled on intestinal wound significantly increased break load
- Additional potential of insertion of a drug-loaded disc between button and rivet, or loading of the rivet with drug

Preliminary Results (solvent cast rings)

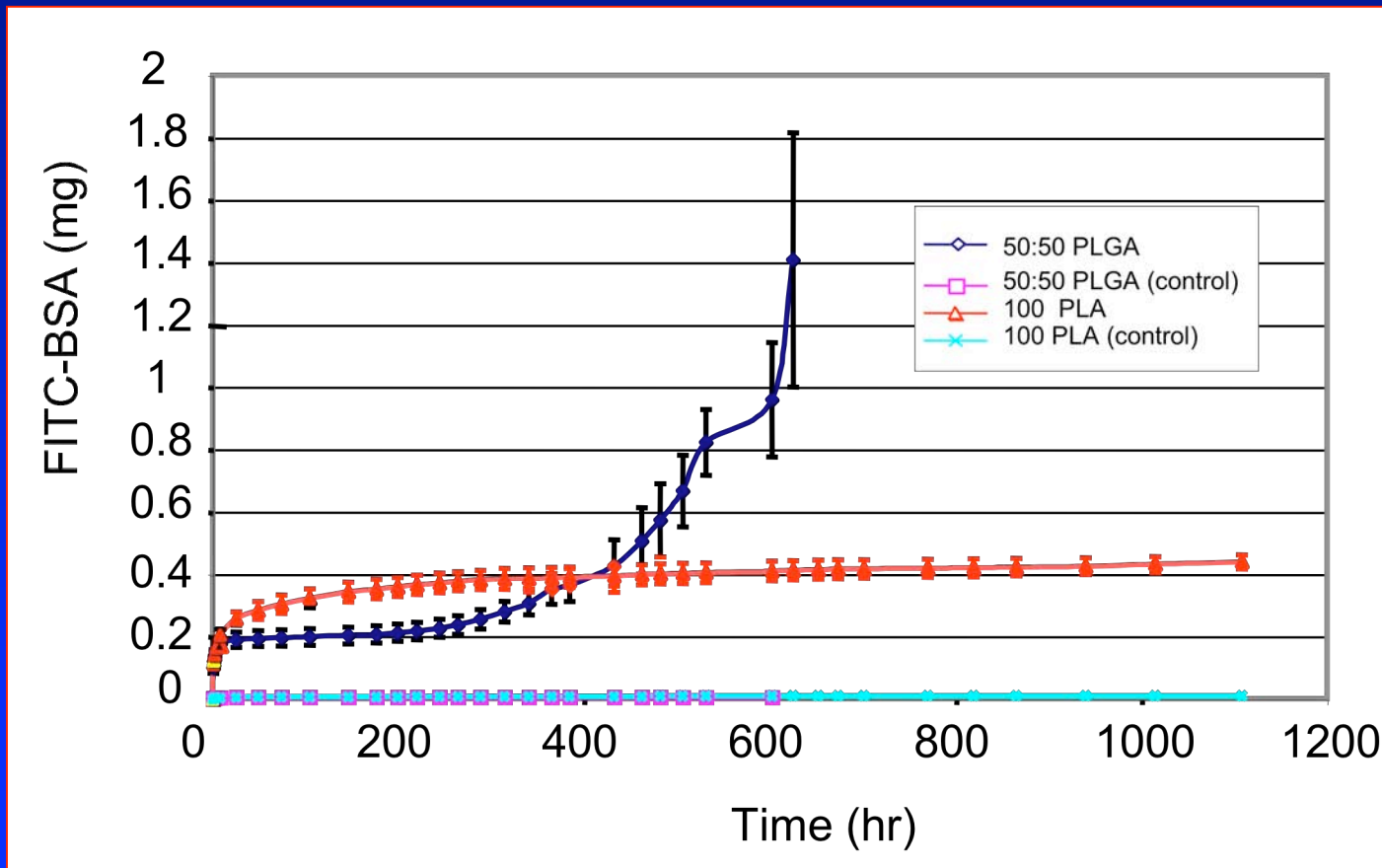


Release of fluorescent albumin in vitro from PLGA, n = 3

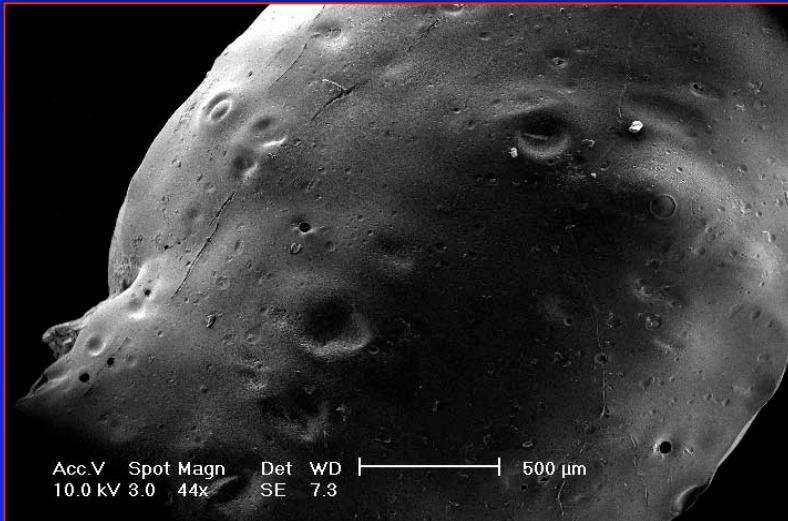
PLGA Extended Time Points



Comparison with PLA



Mode of Degradation



- Surface pitting evident at 14 days with 50:50 PLGA
- PLGA bulk erosion but release profile smooth
- PLL large release starting at 100 days
- Potential of profile selection
- Disc integrity good for >2 weeks. Controllable

Possible FDA Approach

- FDA combination device class III
- PMOA is device (similar to drug eluting stent)
- Pathway is:
 - proof of concept in vivo (now)
 - finalize formulation (1 year)
 - File RFD - animal trials with prototype formulation
 - efficacy and safety (1-2 years)
 - animal trials with complete device
 - efficacy and safety (1-2 years)
 - File IDE (0.5 year)
 - Clinical trials
 - efficacy and safety (2 years)
 - PMA (1 year)

Business Plan

- Patent filed May (2003)
- Build value of IP with *in vivo* data (2006)
- Licensing deal or sale to major surgical supply company J&J or Tyco
- If not, file RFD fundraising, and continue to develop *in vivo* data with further efficacy trials and prototype development (2009)
- Shop the concept again
- If not sold/licensed, File IND, fundraising, and begin clinical trials (2011)

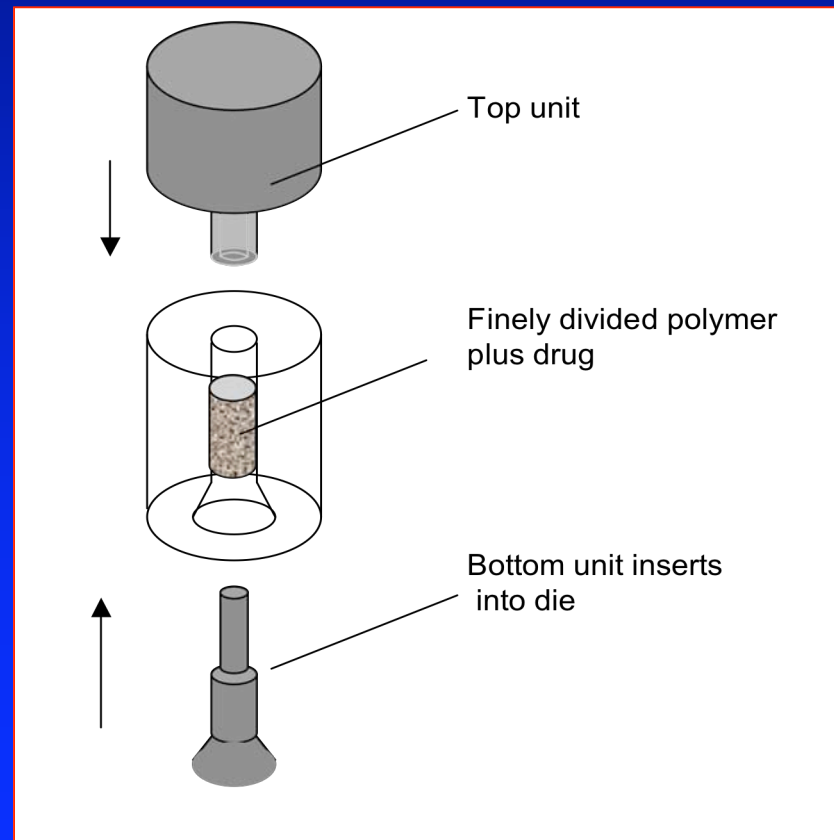
Precedent

- J&J has an absorbable product line:
 - Suture – Monocryl, Vicryl, PDS
 - Clips and anchors – Absolok, bio-Intrafix, Spiralok
 - Staples – (not currently listed)
- J&J has absorbable combination products:
 - Hemostatics - Surgifoam, Surgiflo, Surgicel
 - Suture - Coated Vicryl
 - Adhesion barrier - Intercede

Project Related Aspects

- Solvent casting produced ring with high degree of variability
- Rate of solvent evaporation critical, even slow rate yielded rings with many bubbles
- First stage of project is to develop better methods
- Investigating compression molding

Compression Molding



Therapeutic Staple

Acknowledgements

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