Learning about the blood coagulation system from the outside and inside with simple, low-cost inorganic materials

Galen D. Stucky
Department of Chemistry & Biochemistry, Materials Department, Program in Biomolecular Science and Engineering
University of California, Santa Barbara

Open Wound Arterial Bleeding – Penetrating Trauma
Average adult male human has approximately 5-6 L of blood
Heart can pump 4-5 L blood/minute
Mortality after 1.6-2 L blood loss
QUICK INTERVENTION PREVENTS DEATH 3-5 minutes or less

J. R. Hess et al., The journal of TRAUMA Injury, Infection, and Critical Care, 2008
Blunt Trauma Trajectory -- internal bleeding & long time line

Coagulopathy: Blood’s ability to clot is impaired
Genetic: How well does your body regulate clotting-anticlotting?

J. R. Hess et al., The journal of TRAUMA Injury, Infection, and Critical Care, 2008

The Challenge

♦ Open wound, rapid response treatment — short time window

Stop arterial hemorrhaging in < 5 minutes by interfacing the blood clotting system with an externally applied agent

♦ Internal bleeding — trauma trajectory — longer time window

Selective, targeted delivery into blood coagulation system — therapeutic

♦ Traumatic Coagulopathy — abnormal propensity toward bleeding

Lethal Triad ← Hypothermia – Acidosis – Dilution
History

As of 2006, still no solution to deaths from open wound arterial bleeding

“Uncontrolled hemorrhage continues to be the leading cause of death due to military trauma and the second leading cause of death in the civilian setting”

Pusateri, Holcomb, Kheirabadi, Alam, Wade, and Ryan, Journal of TRAUMA Injury, Infection, and Critical Care, 2006; 60, 674

The Starting Point – State of the Art
Open Wound Arterial Bleeding 2004-2006

Dehydrated zeolite hemostatic agent achieves 100% survival in a lethal model of complex groin injury in swine

Alam, Burris, DaCorta, Rhee  Military Medicine 2005, 170, 63

Sent to Iraq for Military Medical Command use
Applied as a particulate powder, QuikClot

Z-Medica Wallingford, CT
Why zeolite for hemostasis?

“QuikClot powder is made of porous minerals called zeolites. The story is that inventor Frank Hursey, who was working with zeolites as sieves to separate gases (N\textsubscript{2} from O\textsubscript{2}), cut himself shaving and applied it to his face on a whim. How it works is still unclear, although it has been approved for clinical use. “There is a whole lot of surface chemistry,” says Huey (CEO Z-Medica). The product also includes calcium ions, catalysts for the body’s clotting process.”

**NaCa\textsubscript{5.5} (SiO\textsubscript{2})\textsubscript{12} (AlO\textsubscript{2})\textsubscript{12}**
- 27 H\textsubscript{2}O (when fully hydrated)
- Surface Area = 571 m\textsuperscript{2}/gm


---

**Air Products**

Commercial separation of N\textsubscript{2} from O\textsubscript{2}

Using Zeolite 5A confined space electrostatic field

**Electric Field**
- 3.22 V/Å @ 2.5 Å
- 5.65 V/Å @ 2.0 Å

**Zeolite Ca 5A**

\begin{align*}
\text{4:1 selectivity} \\
\end{align*}
A Problem

\[ \Delta H_{\text{hydration}} = 680 \text{ J/g}! \]

2\textsuperscript{nd} and 3\textsuperscript{rd} degree burns on application

Zeolite Ca 5A

Frank Tsung's Experiment

How does it stop bleeding?

Cauterization?
Ca\textsuperscript{2+} delivery?

Hemostasis without burns?

NaCa\textsubscript{5.5}(SiO\textsubscript{2})\textsubscript{12}(AlO\textsubscript{2})\textsubscript{12}\cdot27H\textsubscript{2}O

(when fully hydrated)

April Sawvel

Sarah Baker

Todd Ostomel
Rapid Response – Open Wound

University -- Medical Research Hospitals -- Industry Collaboration

April Sawvel
Todd Ostomel
Sarah Baker
UCSB

Dr. Michael B. Given
Program Officer - Combat Casualty Care
Office of Naval Research
Hasan B. Alam, M.D.
Mass General Hospital
Harvard Medical School
Dr. Richard McCarron
Naval Medical Research Center

Bijan S. Kheirabadi, PhD
Michael R. Scherer, MA
J. Scot Estep, DVM,
Michael A. Dubick, PhD,
John B. Holcomb, MD

Institute of Surgical Research
Fort Sam Houston

Giacomo Basadonna, M.D.
University of Massachusetts
Medical School
Raymond J. Huey
Denny Lo

Z-Medica

Interface Bioprocess Control of Blood Clotting Cascade

2004

Stucky Research Group
Material Synthesis
Interface Control Design
In-Vitro Blood Testing

Naval Medical Research Center
Secondary In-Vitro Testing
In-Vitro Protocol Validation
Swine Model In-Vivo Testing

Z-Medica
Product Development
Packaging
In-Vivo Testing - FDA

Field Use

Starting in 2007

Institute of Surgical Research
Fort Sam Houston
Two effective ways to tune heat release

Increasing Pre-Hydration

0% 10% 20% 40% 80% 100%

0.37% Ag-Exchanged Zeolite 5A

Optimal Pre-Hydration Range

Antibiotic Activity

F1:Ag$_{1.308}$Na$_{0.230}$Ca$_{5.230}$(SiO$_2$)$_{12}$(AlO$_2$)$_{12}$•xH$_2$O

Zone of No Growth Surface Area: Pellet Geometric Surface Area after 24 hours ~ 2.2 cm$^2$ for Ag-exchanged LTA-5A
Antibiotic Activity as a function of Ag content

Ag ion delivery

Could still be sufficient for protecting some wounds


In Vitro Testing UCSB

Haemoscope® Thrombelastograph

R = Clotting Time
\( \alpha = \) Rate of Clotting
MA = Clot Strength
Clotting times in whole blood decrease with increasing temperature

Thermal Imaging and Heat Release

NaCa$_{5.5}$(SiO$_2$)$_{12}$(AlO$_2$)$_{12}$•xH$_2$O

Optimal Pre-Hydration Range
3 to 5 wt %
42 to 45 °C
Dehydration effect

<table>
<thead>
<tr>
<th>Sample</th>
<th>R (minutes)</th>
<th>α (degrees)</th>
<th>MA (mm) Displacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Alone</td>
<td>10</td>
<td>53.4</td>
<td>72.7</td>
</tr>
<tr>
<td>Dry Zeolite</td>
<td>1.4</td>
<td>74.0</td>
<td>71.4</td>
</tr>
<tr>
<td>OHydrated Zeolite</td>
<td>2.8</td>
<td>65.4</td>
<td>70.3</td>
</tr>
</tbody>
</table>

**In Vivo Testing**

Uniformed Services University Hospital, Bethesda, MD

In Vivo Simulated Traumatic Swine Injury Testing

In Vitro Parameters and In Vivo Performance

Selection Criteria for Hemostatic Agents

Field conclusion --- Not good enough!

Need better in vivo and field survivability


What Next?

How might the inorganic agent “control” the blood clotting cascade biosystem?
Inorganic Control of a BioProcess—Abalone shell growth

Abalone flat pearl

Growth on MoS$_2$

growth surface
nacreous aragonite
spherulitic aragonite
green organic

transparent organic sheets (140nm)

prismatic calcite
oriented calcite blocks

large $\Delta G_{\text{crystal}}$

Growth on calcite or glass substrate


Interface with Blood Clotting Cascade System?

- Coagulation
- Fibrin Formation
- Anti-Coagulation

> 220 factors
> 300 interactions

Warfarin, heparin
Dilutional coagulopathy
Acidosis pH < 7.35
Hypothermia

Jeff Varner          Cornell
Mitchell Cohen   UCSF
Mol. BioSyst. 2010, 6, 2272
Frank Doyle     UCSB
Linda Petzold   UCSB
Factor XII and Tissue Factor Interface with the blood clotting cascade?

Negligible Decrease in CT without FXII

Interface with the blood clotting cascade?

No Clotting

Time to Clot Initiation (Minutes)

Platelet-poor plasma

AM Sawvel, SE Baker and GD Stucky, 2007

Autoactivation of FXII on surface
Clotting in the Presence of Heparin

Therapeutic Inorganic System Components

High Surface Area Material Systems
- Heat Release
- Electrolyte Transport
- Pore Structure
- Surface Area
- Surface Charge in Media
- Acidity - Basicity
- Surface Functionality
- Band Structure
- Particle Size
- Particle Morphology
- Protein Delivery/Release
- Antibiotic Delivery
- Enzyme Support Activity
- Cytotoxicity

References:
- Chem Mater (2007) 19, 4390
Target: Define Response of Expanded Total System

Blood clotting cascade system + Therapeutic? inorganic System

Researchers (Naval Medical Research Center) test inorganic coated gauze on an anesthetized pig

Effect of Varying the Guest Cation on Clotting Response

\[ \text{Na}^+ \rightarrow \frac{1}{2} \text{Ca}^{2+} \]

\[ \text{K}^+ \rightarrow \frac{1}{2} \text{Ca}^{2+} \]

AM Sawvel, SE Baker, and GD Stucky
Electrolyte Delivery and Take Up

Increasing Ca$^{2+}$ take up
Decreasing electric field

Zeta Potentials, pH and Ca$^{2+}$

pH in CaCl$_2$(aq) electrolyte

Todd A. Ostomel, Qihui Shi, Peter K. Stoimenov, and Galen D. Stucky
Langmuir 2007, 23, 11233
**Time to Initiate Coagulation and Isoelectric Point (IEP)**

![Graph showing the relationship between isolectric point (IEP) and time to initiate coagulation for different oxides.](image)


table

<table>
<thead>
<tr>
<th>Oxide</th>
<th>IsoElectricPoint (IEP)</th>
<th>R (Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiO$_2$:Fe$_2$O$_3$</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>TiO$_2$</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>SiO$_2$</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>NiO</td>
<td>10</td>
<td>8</td>
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<tr>
<td>Al$_2$O$_3$</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>ZnO</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>

**In Vitro Activity with Different Oxides**

![Graph showing the comparison of in vitro activity with different oxides.](image)


table

<table>
<thead>
<tr>
<th>Oxide</th>
<th>R (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyapatite</td>
<td>25</td>
</tr>
<tr>
<td>ZnO</td>
<td>20</td>
</tr>
<tr>
<td>CuO</td>
<td>15</td>
</tr>
<tr>
<td>NiO</td>
<td>10</td>
</tr>
<tr>
<td>Al$_2$O$_3$</td>
<td>5</td>
</tr>
<tr>
<td>Blood</td>
<td>0</td>
</tr>
<tr>
<td>CaCO$_3$</td>
<td>25</td>
</tr>
<tr>
<td>P25</td>
<td>20</td>
</tr>
<tr>
<td>SBA-15</td>
<td>15</td>
</tr>
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<td>CaO</td>
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<tr>
<td>Zeolite</td>
<td>5</td>
</tr>
<tr>
<td>Glass Beads</td>
<td>0</td>
</tr>
<tr>
<td>Mesoporous Bioactive Glass (MBG)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Notes:**

MBG: Mesoporous Bioactive Glass

- Homogeneous Composition
- High Surface Area

Ostomel, Shi, Stucky "Oxide Hemostatic Activity" J. Am. Chem. Soc. 2006, 128, 8384
Target Parameters for First Responder Field Use

- Rapid response < 5 minutes major arterial bleeding
- Thermal Optimization of Hemostasis
- High Surface Area Efficacy
  - Light Weight
  - Antibiotic Delivery Agent
  - Therapeutic Delivery Agent - wound healing
  - Presentation of surface to support thrombosis
- Electrolyte Control (e.g., Ca$^{2+}$), pH Control
- Active in Presence of Heparin/Coumadin
- Biocompatible (FDA)
- **High Volume, Low Cost, Available, Simple**

Layered clays as heat free hemostatic agents? Yes and No ....

Dehydration of layered clay does not improve effectiveness

Surface Charge in SBF Does!!

Smectites & Saponites – Swellable Clays very Cytotoxic

Why?

Exfoliation!

Extensive animal Testing at San Antonio Army Medical Command Research Center

Kaolinite - $\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})_4$ Non-swellable – high charge

DL Bish, 1993, Clays Clay Minerals 41:738
No Heat!
At same or lower dosage.

Total Hemostasis Time

Kheirabadi, Scherer, Scot Estep, Dubick, Holcomb

Becomes hydrated

* p<0.05

Dehydrated Zeolite
Others
Kaolin

Current Version
Civilian and Military Use

QuikClot
COMBAT GAUZE
For Temporary Exsanguination Control to Traumatic Bleeding

NORTH AMERICAN RESCUE INCORPORATED
Comparative Testing of Hemostatic Dressings in a Severe Groin Hemorrhage

ATACCC presentation
St Pete, FL 10-13 Aug 2008

Trauma & Resuscitative Medicine Department, NMRC
Silver Spring, MD
Department of Surgery, USUHS
Bethesda, MD

New dressings
InstaClot
ACS+
HemCon
CELOX
FP-21
Chitoflex
X-Sponge
Woundstat
Alpha Bandage
BloodStop


“CG (Kaolin) was the most effective dressing tested in this arterial hemorrhage model. CG is now recommended as the first line of treatment for life-threatening hemorrhage on the battlefield….”

From Iraq to Now (2016)

“Thus far I've trained all 350 of the … soldiers on the quickclot and CAT tourniquet. I cannot begin to express to you how grateful we are for your generosity and kindness. These dressing do make a difference on the battlefield. Patients that come into the EMT with quickclot in position from early injury have had 100% survival rate.”

Multiple saves reported from many other places

A police officer in Spokane, WA used QuikClot® 1st Response™ brand to save a man after the police officer himself shot the man in the abdomen after the man lunged at him with a knife. Seven saves documented by the Hillsborough County Sheriff’s Office in Florida, three in the Hudson Valley of New York, and many more.

With permission, Ray Huey, Z-Medica
2008 Top Ten Inventions

Dr. Galen Stucky
Invention
Combat Gauze for Treating External Hemorrhages in Injured Soldiers

“CG is now recommended as the first line of treatment for life-threatening hemorrhage on the battlefield…”

U.S. Army Institute of Surgical Research

Arterial Bleeding Project Begins

2004

Committee on Tactical Combat Casualty Care (CoTCCC)

2007

CoTCCC recommends QCG for use by US military

2008

2013

FDA approves QCG for topical surgical wound/traumatic bleeding

2014

Coagulating and anticoagulating inorganic agents developed

2015

In vivo and in field studies comparing hemostatic efficacy – QCG most effective

Civilian intraoperative use of kaolin-based hemostatic agent

QCG effective in presence of hemodilution and hypothermia

QuikClot Combat Gauze and QuikClot Hemostatic Dressing (QCG)

Committee on Tactical Combat Casualty Care (CoTCCC)

A Solution For First Responders

Military Health System Research Symposium, August 2013

• Field conditions
  – Austere
  – Limited infrastructure
  – Extreme temperatures and conditions

• Desired product
  – Light, portable and deployable
  – Ease of use down to individual Soldier level
  – Example: Combat Gauze carried in each Soldier’s Improved First Aid Kit (IFAK) (weighs one pound)

Standard Issue

<table>
<thead>
<tr>
<th>NSN</th>
<th>NOMENCLATURE</th>
<th>UNIT PACK QTY</th>
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<tr>
<td>8465-01-531-3647</td>
<td>100 Round SHIV/Utility Pouch, MOLLE II</td>
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<td>6515-01-521-7976</td>
<td>Tourniquet, Combat Application</td>
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<td>6530-01-492-2275</td>
<td>Bandage Kit, Elastic OR</td>
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<td>6530-01-560-0849</td>
<td>Bandage Kit, Elastic</td>
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<td>6530-01-509-3117</td>
<td>Bandage GA4-1/2&quot; 100's</td>
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<td>6530-00-926-8883</td>
<td>Adhesive Tape Surg 2&quot; 6's PG</td>
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<td>6515-01-380-0467</td>
<td>Airway, Nasopharyngal</td>
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<td>6515-01-519-9161</td>
<td>Glove, Patient Exam 100's</td>
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<td>6545-01-586-7691</td>
<td>Contents Kit, IFAK Resupply Kit</td>
<td>1</td>
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<tr>
<td>6545-01-531-3147</td>
<td>Insert (holding panels with cord)</td>
<td>1</td>
</tr>
<tr>
<td>6550-01-562-3325</td>
<td>Dressing, Combat Gauze</td>
<td>1</td>
</tr>
</tbody>
</table>

*The Combat Gauze has a 36-month shelf life, so it is shipped separately.
QCG Remains Hemostatic Choice in 2014

- QuikClot Combat Gauze® (QCG) reaffirmed by Committee on Tactical Combat Casualty Care (CoTCCC) as hemostatic dressing of choice
- More than 5 million units of QCG shipped to five branches of US Military by Z-Medica
- No product-related adverse reactions reported

A better performing candidate

Mesocellular Foam

**Clotting time MCF-33 ≈ Combat Gauze at a significantly lower dose**

- **Clotting Time (Minutes)**
- **20 mg Kaoiin**
- **2 mg MCF-33**
- **2 mg MCF-33 Thrombin**

**Decreased Clotting Times in both Normal and Coumadin Plasmas**


---

**MCF @ thrombin activates clotting through the contact pathway**

- **Clotting Time (Minutes)**
- **No Clotting**

Silica-based particles (MCF) are less cytotoxic than aluminosilicates (zeolites and kaolin)

Cellular uptake after overnight exposure

IC50 was determined after overnight exposure of the cells to mesoporous silica and kaolin.


Blunt Trauma Trajectory -- Internal bleeding & long time line

Coagulopathy : Blood's ability to clot is impaired
Genetic: How well does your body regulate clotting-anticlotting?

Coagulopathy
Fundamental breakdown of the human coagulation cascade system

“In Trauma Triad of Death”

Inability to Maintain Normal Hemostasis
Need early predictors of mortality – fast therapeutic response decisions

anaerobic metabolism & lactic acid production

Factors That Influence Traumatic Coagulopathy
ACoTS: Acute Coagulopathy from Traumatic Shock

Parr, Michael J. et al. J. Trauma, 2008, 65, 766

Threshold switchable particles for control of internal hemorrhage

Stephanie A. Smith DVM MS
University of Illinois College of Medicine

James H. Morrissey
Molecular & Cellular Biology
Department of Biochemistry
University of Illinois

Rustem Ismagilov
California Institute of Technology

Ying Liu
University of Illinois Chicago

Damien Kudela
Chi Nguyen
Anna May-Masnou
Alessia Pallaoro
Tracy Chuong
Scott Hammond
Galen Stucky
Gary B. Braun
Erkki Ruoslahti

UCSB & Burnham Institute for Medical Research

Christian Kastrup
University of British Columbia
For Internal Bleeding Cardiovascular Targeting and Delivery

Thrombin or prothrombin are strong coagulating agents – what about

- Thrombosis
- Biodistribution ??

WHAT IF WE HAD

Threshold switchable particles for the control of internal hemorrhage?

No need for packaging or encapsulation!

Polyphosphate (PolyP)

Linear polymer of phosphate units

Stephanie A. Smith, James H. Morrissey
Polyphosphate in Platelets

PolyP secreted by platelets in response to thrombin stimulation

Ruiz FA, Lea CR, Oldfield E, Docampo R.
Human platelet dense granules contain polyphosphate and are similar to acidocalcisomes of bacteria and unicellular eukaryotes

J Biol Chem 2004; 279(43):42250-57
Platelet polyP is a poor coagulator for normal blood


Thrombin Generation with Tissue Factor Added

Smith, Morrissey
Coagulation and reduced fibrinolysis with PolyP

Smith, Morrissey

FV Activation

PolyP enhances the rate of cleavage of FV to FVa by both FIIa & FXa

Smith, Morrissey
Simplified Schematic of Blood Clotting Cascade System

Intrinsic Pathway (Contact Activation)
Open Wound

Extrinsic Pathway (Internal)
Vascular Injury

Factor VII, VIII, XI Activation
Prothrombin (II)

Common pathway

Platelet Activation
PAR Signalling
Factor XIII Activation

Prothrombin

Thrombin

Cell Signalling

Procoagulant
Anticoagulant

* 60-100 mers (accelerates V, VIII, X, XI)
PolyP -- Internal BCS accelerated formation of Thrombin/Fibrin via PolyP

What else?

Effect of polyP on clot structure

Smith, Morrissey
Fibrin Tissue Sealant

No PolyP  + PolyP

Smith, Morrissey
How can we make point-of-care & clinical use of PolyP?

- As an accelerator of blood clotting cascade system at trauma sites only

- As a means of defining the trauma trajectory to minimize “lethal triad” and coagulopathy
Strategy for functionalization: targeting & protection

SiO₂ NP’s
pKₐ 7.6 to 8.4
pK₇ 1.9

Phosphates
- orthophosphate: 2.15, 7.20, 12.35
- pyrophosphate: 0.8, 2.2, 6.7, 9.4
- tri(poly)phosphate: 0.5, 1.0, 2.4, 6.5, 9.4

Strategy for functionalization: targeting & protection

1. Amino-group
2. Linker
3. Peptide
4. PEG

Covalent functionalization

Nguyen, Kudela, Masnou, Stucky
Strategy for functionalization: targeting & protection

Steps of functionalization: clot time increases with PEG

Nguyen, Kudela, Masnou, Stucky
Thrombin generation: plate reader

Thrombin-sensitive dye Boc-Asp(OBzl)-Pro-Arg-MCA

- Coumarin derivative C120 exhibits fluorescence

Kudela, Masnou

Polyphosphate-coated silica nanoparticles (SNP-P70) have lower clotting time than SNP

Kudela, Masnou
Polyphosphate coated silica nanoparticles (SNP-P70) are similar to kaolin and better than polyP in solution.

SNP-P70 stimulates and accelerates clotting: synergistic effect.
PolyP-SNP is stable at ambient conditions

PolyP promotes coagulation in FXII deficient plasma

Coagulopathy - The fundamental breakdown of the human coagulation cascade system

"Trauma Triad of Death"

Inability to Maintain Normal Hemostasis

Need early predictors of mortality – fast therapeutic response decisions

anaerobic metabolism & lactic acid production

Factors That Influence Traumatic Coagulopathy
ACoTS: Acute Coagulopathy from Traumatic Shock

Parr, Michael J. et al. J. Trauma, 2008, 65, 766

Testing the nanoparticles under coagulopathic conditions: the “lethal triad” trauma trajectory
Hemodilution: TEG results

Hemodilution – Thrombin Production

Kudela
Acidosis – TEG

Acidosis – Thrombin Production
Hemostasis & Temperature

Hypothermia induced coagulopathy?

Disregulation of clotting factors and platelets


Hypothermia - TEG results
Hypothermia – thrombin production

polyP-SNP

Thrombin Generation (R.F.U.)

Time (min)

32°C

Thrombin Generation (R.F.U.)

Time (min)

Take home message

Inside BCS therapeutic with PP triggering

Active Ingredients: Polyphosphate & pro- or non-coagulating carrier (e.g. SiO₂ or hydroxyapatite)

Biocompatibie

Uses materials that minimize harmful side effects

Directs trauma trajectory away from coagulopathy

Expands dilution, hypothermia, acidemia windows

Universal use

Can be modified to treat external and internal bleeding
Collaboration with Chi Nguyen (Stucky lab) and Kyle Ploense (Kippin lab)

Translating polyP-SNP into clinical use

Proof of concept
Safety, efficacy

Complex model
Efficacy
Safety
FDA IND

Clinical Trials

Histopathology Reports (Charles River): no thrombi, no clear microthrombi, no vascular changes, and no necrosis.

Safety studies show no thrombosis

ICP-MS conducted by Chi Nguyen (Stucky lab) in collaboration with Kyle Ploense (Kippin lab)
PolyP-SNP reduces blood loss 33 % after tail injury (p = 0.0097)

PolyP-SNP reduces overall clot size by forming smaller, denser clots directly at the wound site (p = 0.074)
PolyP-SNP quickly stops all blood loss ($p = 0.0005$)

The Challenge and Where We Are

- Open wound, rapid response treatment --- in the field
- Stop arterial hemorrhaging in < 5 minutes by interfacing the blood clotting system with an externally applied agent
- Internal bleeding - trauma trajectory - create a longer time window for 1st responders and clinicians (*in vitro*)
  - Lethal Triad $\rightarrow$ Hypothermia – Acidosis – Dilution
- Traumatic Coagulopathy – can accelerate total blood clotting system with targeted, non-procoagulating, therapeutic delivery (*in vitro*)
What Next?
Translation of polyP-SNP into clinical use

**UCSB – Cayuga Inc.**
- Synthesis polyP-SNP
- *In vitro* clotting assays
- Adapt polyP-SNP preclinical and clinical trials

**Small mammal studies**
- UCSF (Cohen lab), UCSB
- *In vivo* proof of concept

**Clinical**
- Use for trauma patients
  (UCSF, Davis, Irvine Huntington Medical Research)

**Preclinical large mammal studies**
- Primates/swine at UC Davis – UC Irvine
- Travis AFB
- Preclinical (human use)

Thanks!