Homeland Defense & Security
Information Analysis Center

Nanotechnology in Combat Casualty Care: State of the Art and Emerging Trends

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Why This Topic? Why Now?

Combat Casualty Care (CCC)

- Trauma life support in prehospital combat medicine
- Reduce mortality and morbidity resulting from injuries on the battlefield
- Shifting from treating injuries in wars of the past to wars of the future
- What are the needs moving forward? How to best leverage technology?

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Nanotechnology

- Science, engineering, and technology conducted at the nanoscale, 1 to 100 nanometers
- Used across all science fields, such as chemistry, biology, physics, materials science, and engineering
- DoD has invested over $5 billion since late 1990s
- Huge research and investment interest in nanomedicine – DoD/VA, academia, and private sector

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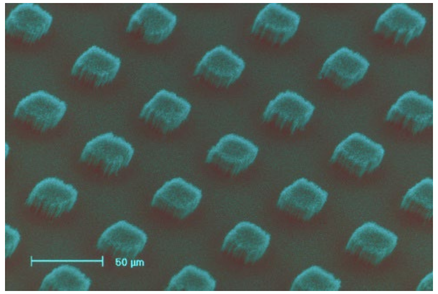

What Are We Trying to Achieve?

- DoD is already investing in this area – nanotechnology for combat casualty care
- What (if anything) is commercially available or being used in the field?
- What is DoD currently funding?
- Are other organizations funding relevant research?
- What are the emerging trends for the near future?
- What are the limitations and challenges of implementing nanotechnology in this area?
- What is the payoff?

Methodology and Limitations

Approach

- Reviewed current structure and research of CCC-oriented programs
- Evaluated peer-reviewed and gray literature (back to ~2019)
- Interviewed subject matter experts
- Utilized in-house expertise and knowledge

Challenges

- Massive amount of information to sift through

Results

- Focused on what is currently used and/or realistically possible - DoD
- Generated general emerging trends in the field and subfields

A Little Icebreaker

Greg's funny (but accurate) takeaways

1. Everybody wants to make something out of chitosan
2. The FDA can be challenging to work with sometimes
3. Just because you can make it from nano...doesn't mean you should
4. Making nano things is REALLY difficult, especially in medicine
5. DoD just needs stuff – doesn't matter how it gets there
6. Some areas are clearly moving further along faster than others

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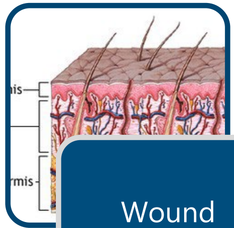
Agenda

Introduction

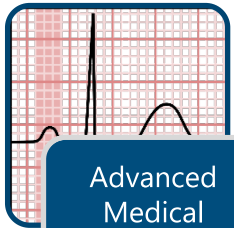
Hemorrhage Control/Fluid Resuscitation



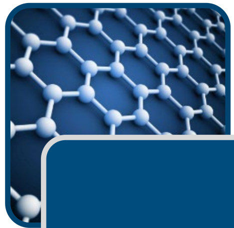
Wound Management and Infection

Tissue Regeneration and Engineering

Neurotrauma and Pain Control



Advanced Medical Monitoring and Diagnostics



Summary

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Hemorrhage Control and Fluid Resuscitation

Blood Substitutes and Hemostatic Agents

What Are We Trying to Do Here?

"Hemorrhage is the leading cause of preventable death on the battlefield."

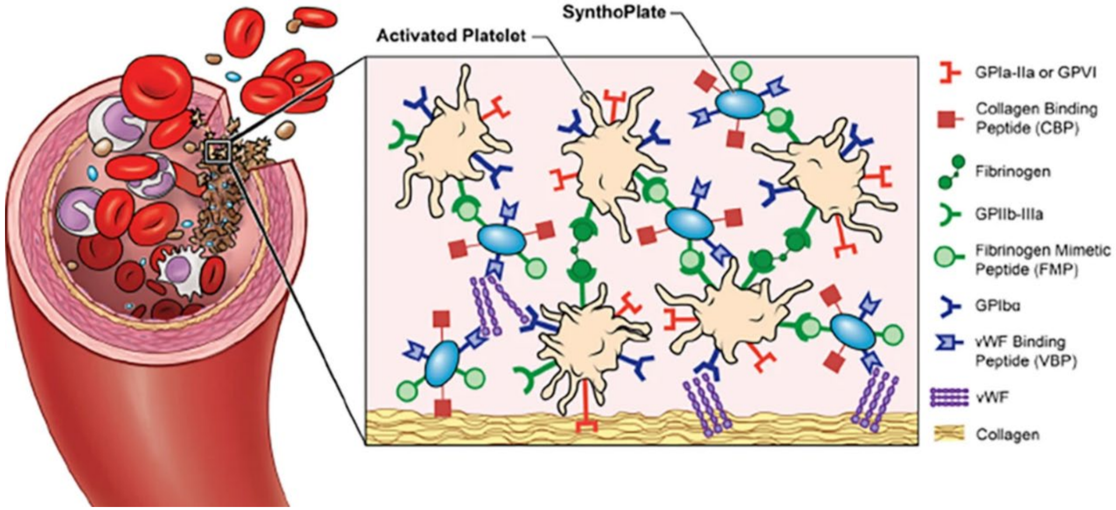
Blood substitutes to address three things:

1. Volume
2. Clotting
3. Oxygen transport

Eastridge B.J., Mabry R.L., Seguin P., et al. Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *J Trauma Acute Care Surg.*, 2012. 73(6 Suppl 5): p. S431-7.

Best Current Technology Examples

SynthoPlate



Hickman, D.A., Pawlowski, C.L., Shevitz, A., et al. Intravenous synthetic platelet (SynthoPlate) nanoconstructs reduce bleeding and improve golden hour" survival in a porcine model of traumatic arterial hemorrhage. *Sci Rep.* 8, 3118 (2018). https://doi.org/10.1038/s41598-018-21384-z. This is an open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

ErythroMer

Synthetic "artificial cell"

- Nano-encapsulated human hemoglobin (0.12 - 0.15 μm)

Bioengineered to mimic RBCs

- Option for all blood types
- Avoids NO trapping
- Biodegradable

Freeze-dried, sterilized product

- No refrigeration
- Rapid reconstitution

https://www.kalocyte.com/erythromer/

Emerging Trends

- Shift from just mimicking function to mimicking structure + function
- All roads lead to viable whole blood alternative

  - DesiCorp
  - DARPA Fieldable Solutions for Hemorrhage with bio-Artificial Resuscitation Products (FSHARP) program
  - U.S. Army Institute of Surgical Research
    - 2035 “paradigm-changing” efforts: engineered dried whole blood alternatives
    - Next generation, extended shelf-life platelets
    - Next generation, extended shelf-life whole blood

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Challenges

- Cost
- FDA Approval
- Immune Response
- Biokinetic Modelling
- Intellectual Property/Design

Wound Management and Infection

Wound Closure, Bandages and Dressings, Infection Control and Prevention, and Burn Care

Current State of Things

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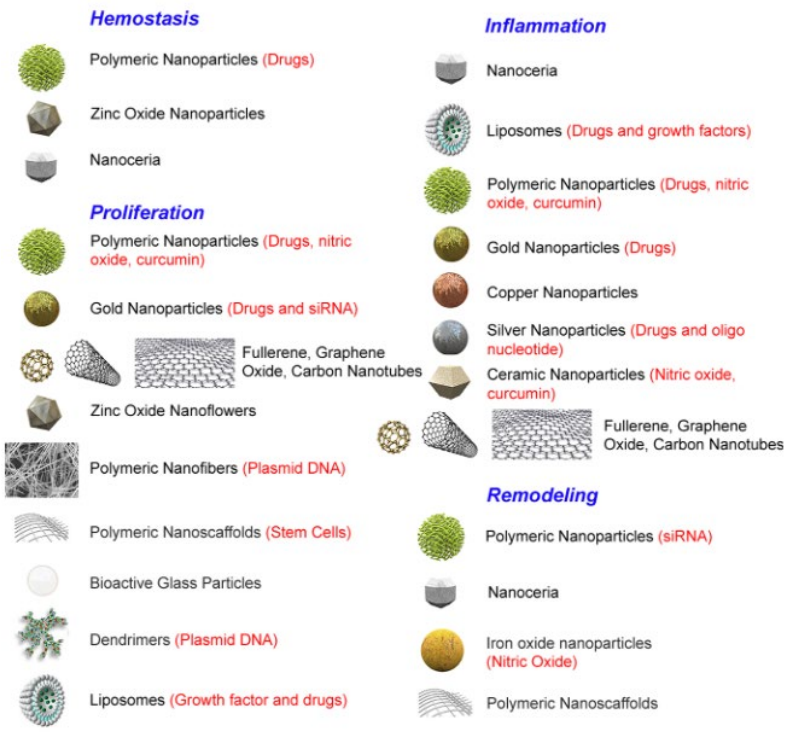
Wound care is like the "wild west"

- 2,000+ products
- No clear market leader
- No clear singular development path or goal
- Nano-based solutions offer incremental change

What's Happening?



Hamdan, S., Pastar, I., Drakulich, S., Dikici, E., Tomic-Canic, M., Deo, S., Daunert, S. (2017). Nanotechnology-driven therapeutic interventions in wound healing: Potential uses and applications. *ACS Central Science*, 3(3), 163–175. https://doi.org/10.1021/acscentsci.6b00371. This is an open access article published under an ACS AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes.

Two main strategies in nano-based materials for wound healing

1. Nanomaterials that are capable of healing as a result of inherent properties of the nanoscale material
2. Nanomaterials as carriers for delivering therapeutic agents

Emerging Trends

- Shift from passive to active dressings
  - Integration of wound management with hemorrhage control and/or promotion of tissue regeneration
  - Dressings with sensing applications
- Continued and growing interest in using chitosan and other biomaterials

Challenges

- No clear, unified goal
- Costs – nanomaterial applications (films, coatings, membranes) tend to be much more expensive than the underlying dressing/bandage itself
- Lots of commercial off-the-shelf applications for chronic wound care but lacking for trauma and acute wound management

Tissue Regeneration and Engineering

Emphasis on Bone

Current Goal in Bone Engineering?

Aim: repair and promote regeneration of new tissue by the combination of three main components:

1. Cells
   - Obtained from a variety of sources: autologous, syngenic, allogenic, and xenogenic
2. Scaffolds
   - Made by materials such as metals, ceramics, and polymers
3. Chemo-physical Stimuli
   - Mechanical, electrical, chemical

Nanostructured Biomaterials

Properties [1]

Mechanical: bone formation response can be changed by altering the mechanical environment

Biocompatibility: biocompatibility of biomaterials play an important role in their performance for bone healing

Osteoinductivity: induces new bone formation

Biomaterials [2]

Nanostructured, calcium-phosphate-based materials

- Nanobioglass
- Hydroxyapatite
- Tricalcium phosphate

Nanocomposites

- Ceramic/polymer composites (e.g., HA/PLGA, HA/alginate)
- Biohybrid composites

[1] https://pubs.rsc.org/en/content/articlehtml/2021/nr/d1nr01371h

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7471872/

Best Available and Emerging Trends

NuShores Biosciences

NuCress™ bone scaffold technology has been shown to promote healing of large segmental bone breaks (>2.5 cm) tested in large and small animals (goats, mice) – with no infections, inflammation, rejection, or adverse bone response [1].

Texas A&M

Research team led by Akhilesh K. Gaharwar developed water-stable, 2D covalent organic framework (COF) nanoparticles that can direct the differentiation of human mesenchymal stem cells into bone cells [2].

Department of Veterans Affairs

Dr. Ripley and her team could get 3D-printed living bone to clinics in three to five years [3].

[1] https://nushores.com/about-us/
[2] https://today.tamu.edu/2022/03/29/engineering-researchers-develop-porous-nanoparticles-for-regenerative-medicine/
[3]https://govmatters.tv/department-of-veterans-affairs-could-get-3d-printed-living-bone-to-clinics-in-three-years/?noamp=available

Challenges

- Engineering of biomaterials that can match both the mechanical and biological context of bone tissue matrix and support the vascularization of large tissue constructs [1]
- High cost

[1] https://www.frontiersin.org/articles/10.3389/fcell.2021.665813/full

Neurotrauma and Pain Control

Traumatic Brain Injury, Neuroprotection and Monitoring, and Pain Management

Current Goals

1. Detect potential adverse impacts to brain
   - ❖ Nanosensors to monitor blast pressure/force
   - ❖ Measuring blood biomarkers of injury
2. Prevent or reduce impact
   - ❖ Rapid administration of therapeutics
     - Pain management
     - Alter inflammatory response

Representative Technology

NanoDx™

- Licensing agreement with IBM Research for use of its metal-oxide, semi-conducive (CMOS) compatible nanosensors
- Patented nanosensor design that includes an array of highly sensitive nanowires that measure electrical resistance and are functionalized with antibodies that bind with target biomarkers
- Detects the presence of biomarker proteins (S100B & GFAP) in blood
- Preclinical study, 100 patient blood samples were tested and resulted in a sensitivity of 100% and 0 false negatives

Emerging Trends

- Nanoparticles to cross blood brain barrier (BBB)
  - Intranasal route
- Alternatives to opioid-based pain management
- Immune modifying nanoparticles (IMPs)
- Nano-based siRNA carriers
- Monitoring protease activity/ECM changes
- Promote tissue regeneration at time of injury

Challenges

- Bioethical issues
- Health and safety – potential toxicity
- Clinical trials – approvals, cost
- Regulatory
- Scalability

Advanced Medical Monitoring and Diagnostics

What's Happening

Goal #1

Move the point of care (POC) to the individual

- ❑ Diagnose AND treat in near-real-time on the person
- ❑ Monitor processes at cellular level

Goal #2

Extend the capabilities of field medical personnel

- ❑ Improve the continuity of care
- ❑ Create a force multiplier for medicine

Best Current Examples

Pioneering tissue-integrating biosensors for continuous monitoring of body chemistries

Legionarius smart garment senses penetrating wounds and burns and automatically creates an ATAK alert and Troops in Contact (TIC) message with the geolocation of the casualty and a data profile of the wound combined with vital signs data from physiological sensors

Emerging Trends

- Graphene becoming a very popular substrate
- Lots of work with implantable sensors, especially in continuous glucose monitoring
- Micro/nanosensors making it possible to monitor biomarkers in sweat and interstitial fluid instead of blood
- Nano in flexible electronics and to make smart fibers for textiles
- Self-powering nanosensors (tribo-/piezoelectric)

Challenges

Ethical issues (especially with implantable sensors)

Bandwidth

Limits on analytes/sources

Cost

Practicality

Developing Trends and Conclusion

Summary and Acknowledgments

State of the Art: Wrap-Up

Category	Current Possibilities	Future Possibilities
Hemorrhage Control and Fluid Resuscitation	Platelets Oxygen Carriers (RBCs) Other hemostatic agents	Whole blood alternatives
Wound Management and Infection	Passive bandages and dressings Bionanomaterials (Chitosan) Antimicrobial coatings/loaded NPs	Realtime wound monitoring Active/responsive dressings
Tissue Regeneration and Engineering	Bone rebuilding	Onsite tissue regeneration for all tissues
Neurotrauma and Pain Control	Measure blast pressure Rapid TBI biomarker assessment	Intranasal delivery route (pain control) On-site CNS injury mitigation
Advanced Medical Monitoring and Diagnostics	Graphene-based sensors Implantable/injectable sensors (glucose) Sweat-/ISF-based approaches	Moving POC to individual – extending the capabilities of field medical personnel (theragnostics) Real-time monitoring at the cellular level (pre-diagnostics)

Universal Trends

1. Shift toward convergence – nanomaterials + biomaterials + 3-D printing + internet of things
2. Paradigm shift from asking for nano-centric solutions to solve problem to just solving problems, and nanotechnology happens to offer better functionality to address those challenges
3. Developing capabilities and interest in liposomes/lipid nanoparticles in all areas
4. Increased utilization/deliver of siRNA
5. Nanotechnology is allowing for an easier crossover of areas =
    - Hemorrhage Control + Wound Management
    - Wound Management + Tissue Regeneration
    - Would Management + Advanced Medical Monitoring
    - Neurotrauma + Advanced Medical Monitoring
    - Neurotrauma + Tissue Regeneration

Challenges

- How do we translate nanoscience into treating combat wounds of the future?
  - Burns
  - New injuries from new weapons
  - Old injuries from old weapons
  - Civilian casualties/humanitarian assistance
  - CBRN threats in conjunction with traditional combat injury concerns
- How do we not overengineer solutions?
- How do we do a better job of using nanotechnology appropriately?
- What safety and ethical issues still need to be addressed?
  - Regulatory pathways
  - Long-term biokinetic modelling (especially nanobiomaterials)
  - Privacy/data security
- What lessons learned from nanotech applications in other fields can be brought to combat casualty care and how?
  - Diabetes care
  - Oncology

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