BINARY HEMOSTATIC “GEMMA”

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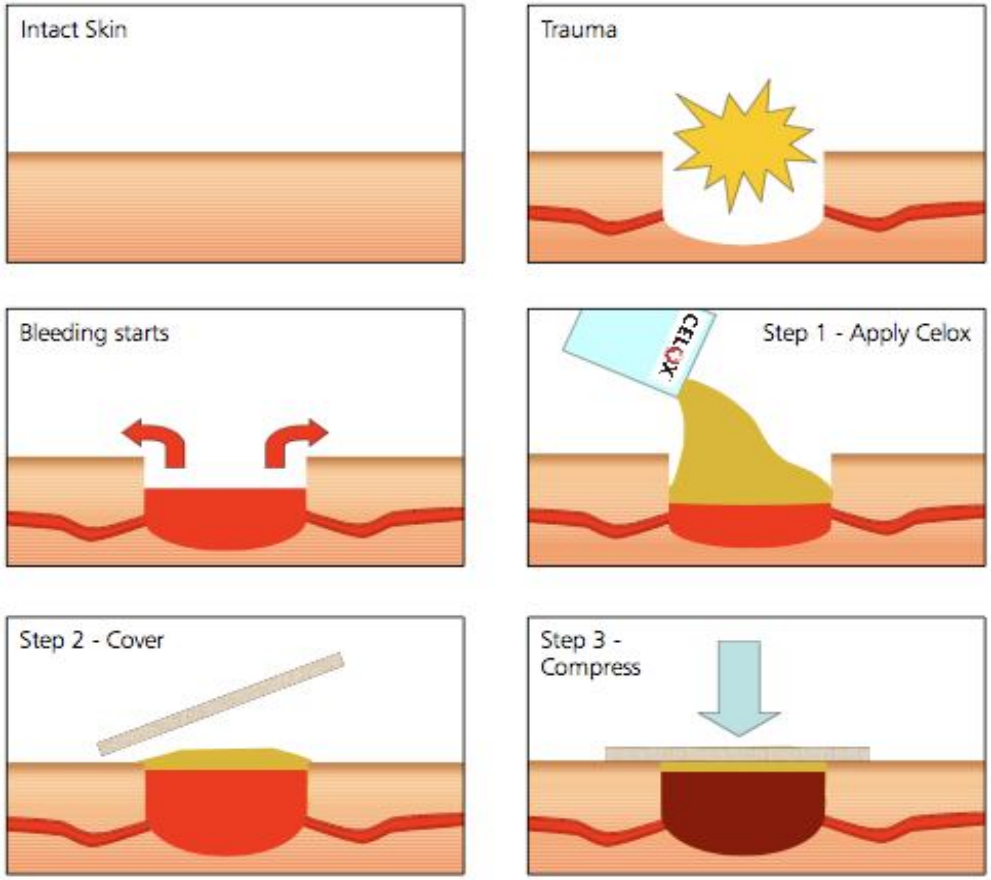
Acute bleeding and consequences.

According to world statistics, since the Second World War up to the present time, the main cause of death up to 60% of the wounded on the battlefield and in emergencies, is a bleeding.

As cited in “Military Times”,
“90 percent of the deaths occurred before the injured soldiers reached a medical facility.”

Kime, Patricia. "Study: 25% of War Deaths Medically Preventable.“ Military Times, 29 Mar. 2013.
https://www.militarytimes.com/2013/03/29/study-25-of-war-deaths-medically-preventable/



Company Background

- NOIGEL LLC is a New York based company, established in 2010.
- **Our mission is to find new and innovative ways to treat unmet needs in medical field and pharmaceutical industry.**

- Executive team:
  - Dr. Boris Farber, Phd. Chief Executive Officer
  - Dr. Ilya Kleyn, M.D. Chief Medical Officer
  - Dr. Artur Martynov, Phd. Executive Vice President of Research
- Key advisors
  - Dr. Daniel Beckles, M.D., Ph.D., FACS, FACC, FCCP
  - Dr. Eduardo Javier Mascareno Ph.D.

Current hemostatics

Celox and QuikClot are the most commonly used hemostatic agents by the military and hospital trauma centers. These hemostatic agents are based on natural polymers.

Current hemostatic composition

The chitosan, alginic acid, kaolin, zeolite and other constituent components.

- **Chitosan** - is a sugar that is obtained from the hard outer skeleton of shellfish, including crab, lobster, and shrimp.
- **Alginic acid –** is a high molecular weight linear polymer isolated from seaweed. It is an acid polysaccharide present in the extracellular matrix of brown algae.
- **Kaolin -** is the mineral kaolinite, a hydrous aluminum silicate. It is part of the group of industrial minerals.
- **Zeolite –** is a granular substance derived from lava rocks**.**

Current hemostatic downsides

Nonabsorbable, loose granules, delaying wound healing and has to be removed.

The exothermic effect of granules occasionally can cause second-degree burns.

Chitosan-based product with nonabsorbable granules may lead to necrosis of the surrounding tissues.

Hemostatic (engorgement effect) cause tight and firm pressure on the bleeding site and may cause necrosis surrounding tissue.

NOIGEL'S Research Project

Research

NOIGEL LLC, Mechnikov Institute of Microbiology and Immunology

Testing Method

Acute bleeding testing in vivo

Intelectual Property IP

NOIGEL has patented pharmaceutical compositions known as "Gemma"

TRIZ and Pharmaceutical Industry

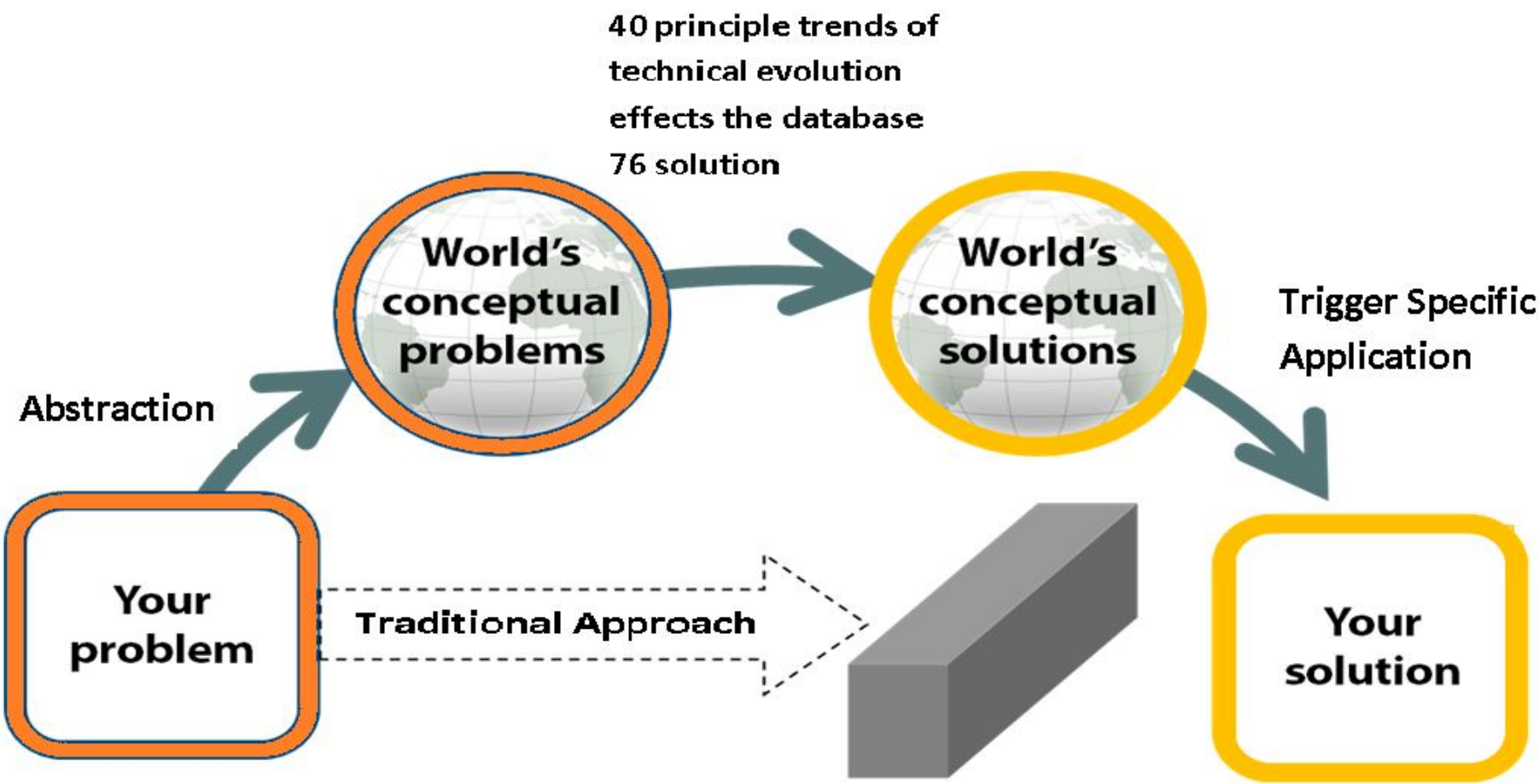
NOIGEL is the only company, which applying TRIZ[1] for all R&D projects in Pharmaceutical industry.

- TRIZ method mainly utilized in Industry of technology, product development, design engineering, process management.

- TRIZ principles have been used in many industries and companies including Samsung[2], General Motors[3] , NASA[4] .

1. https://zenodo.org/record/2547580#.XKKKmJhKhPa
2. **Forbes** https://www.forbes.com/sites/haydnshaughnessy/2013/03/07/why-is-samsung-such-an-innovative-company/#2e46fdb02ad7
3. https://triz-journal.com/axiomatic-design-triz-compatibilities-contradictions/
4. http://www.xtriz.com/publications/AccelerateInnovationWithTRIZ.pdf

PRISM OF TRIZ



Hypothesis

New hemostatic:

- Substance must quickly stop the bleeding, by tight and firm pressure on the bleeding site without consequences on surrounding tissue.
- Should be used in small amount and same time should be able to cover different type of wounds and wounds sizes.
- New hemostatics should not be immunologically rejected by the body.
- Should have the capability of resorption and metabolites safely eliminated from the human body. After applying to bleeding site, no need for physical clean out (removal).

TRIZ contradictions in Hemostatics

- The first TRIZ contradiction:
  From one side, a new substance must quickly stop the bleeding and the tamponade must be tight and firm, on the other hand the rapid and firm pressure on the bleeding site may cause ischemia and necrosis of compressed healthy tissues. To avoid that tamponade must be firm and same time must not be firm.

- The second TRIZ contradiction:
  On the one hand, in order to stop severe bleeding from multiple injuries, we would need to use a large amount of hemostatic substances, because the volume of the wound is equal to the volume of the powder placed in the wound; on the other hand, it is difficult to carry a large amount of substance on the battlefield. Hemostatic substances should be a small amount and should be big enough to cover large wound at the same time.

TRIZ principles to solve problem

The principle of Rejection and Regeneration: which is briefly defined as: when having fulfilled its purpose or become an unnecessary part, an object must be discarded. In this case, it meant the complete biodegradation of an artificial thrombus or its parts after the function has been performed, even if then a fragment of an artificial thrombus will remain in the wound

The principle of Self-organization: In the self-assembly of the active substance from inactive precursors, a gel-like implant is formed from two dry components in the mixture in the presence of blood. The terminal fragments of these components are firmly attached to the wound edges, tightening them and preventing rebleeding.

The principle of Dynamism: this principle states the characteristics of the object should be changed to be optimal at each stage of work. In our case this meant that for different sizes of wounds the same dose of the drug should help, and only the percentage of absorbed blood would change dynamically.

Current biodegradable polymers

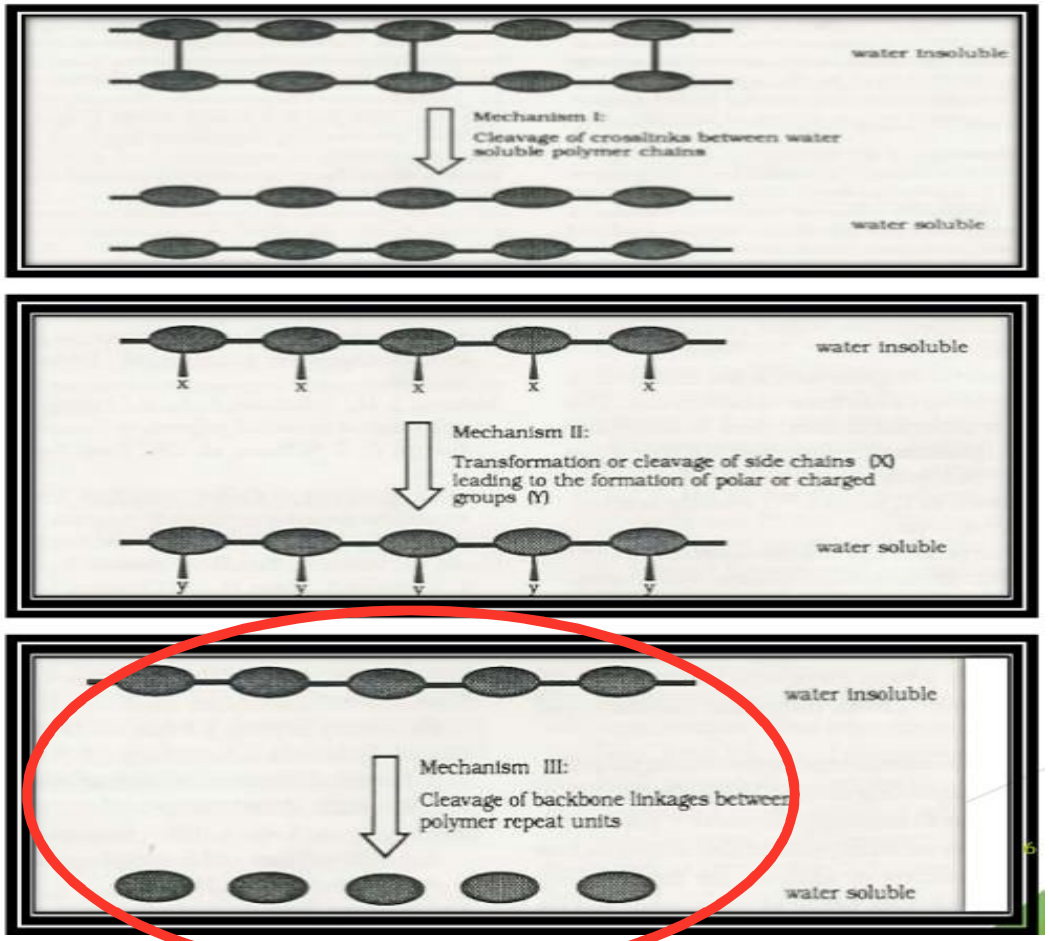
BIODEGRADABLE POLYMERS

- Biopol
  (Polyhydroxybutarate-hydroxyvalerate)
- Polycaprolactone
- Polylactic Acids
- Polyglycolic Acids
- Polydioxane

Most common mechanisms of biodegradation

Enzymatic Degradation

- ✓ Mechanism I
  Cleavage of Crosslinks
- ✓ Mechanism II
  Transformation of Side Chains
- ✓ Mechanism III
  Cleavage of Backbone



Stages of studies and discovery of novel Hemostat

1. Selection of polymers with high adhesive properties to the vascular endothelium.

2. Pharmacological compounds based on the polymers structure and response to bleeding.

3. Pharmacological study of compounds designed to model in vitro interaction of hemostat with bleeding blood vessels recording rate of polymer swelling and time necessary for clot formation. Additionally Time necessary for clot dissolving without recurrence of bleed was measured

4. To discover the best candidates for compounds in vivo major bleeding model in larger animals (rats, rabbits, pigs).

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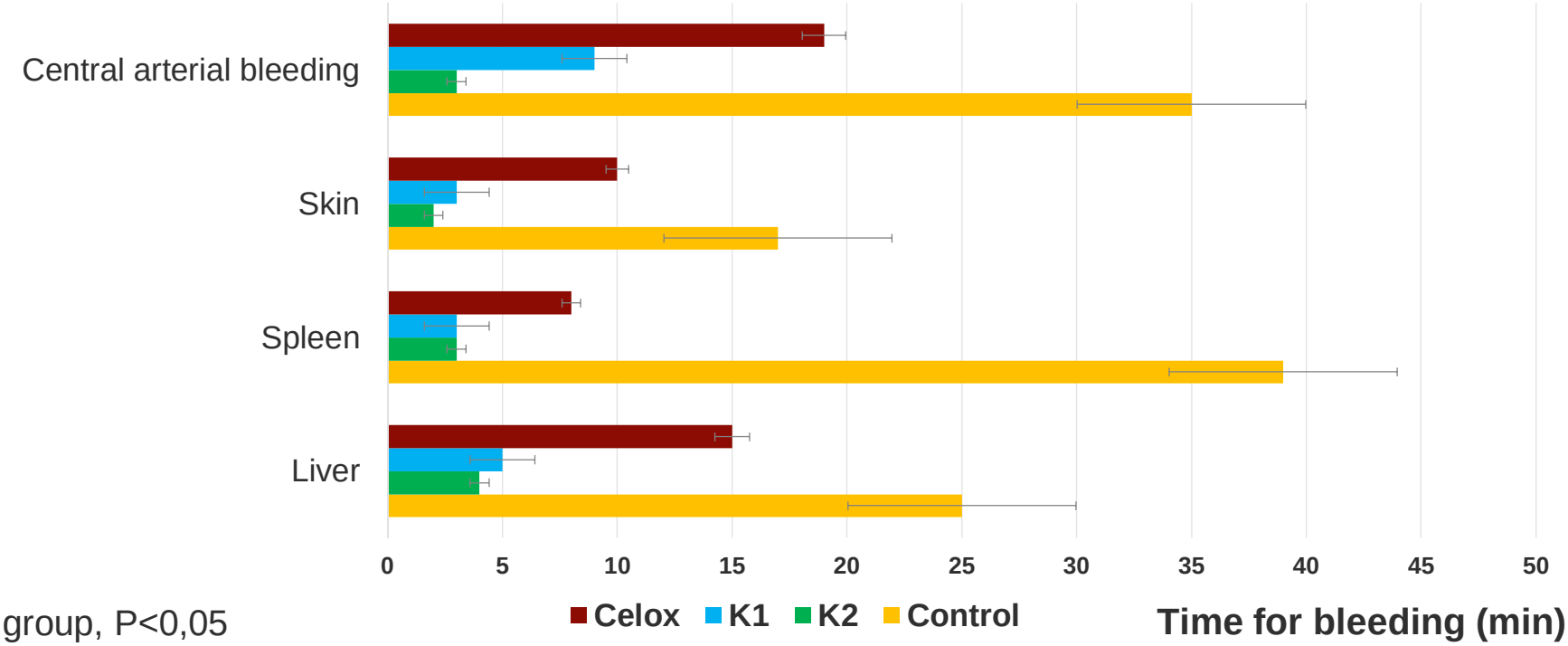
Noigel's Discovery Gemma (K1, K2)

- Using computer mathematical modeling and TRIZ principles, Noigel discovered Gemma compositions, K1 and K2.
- K1 and K2 are binary hemostatic compositions with high adhesive properties to the vascular endothelium.
- Gemma compositions (K1 and K2) are biodegradable ,water soluble, and eliminating from the body without a detectable trace.

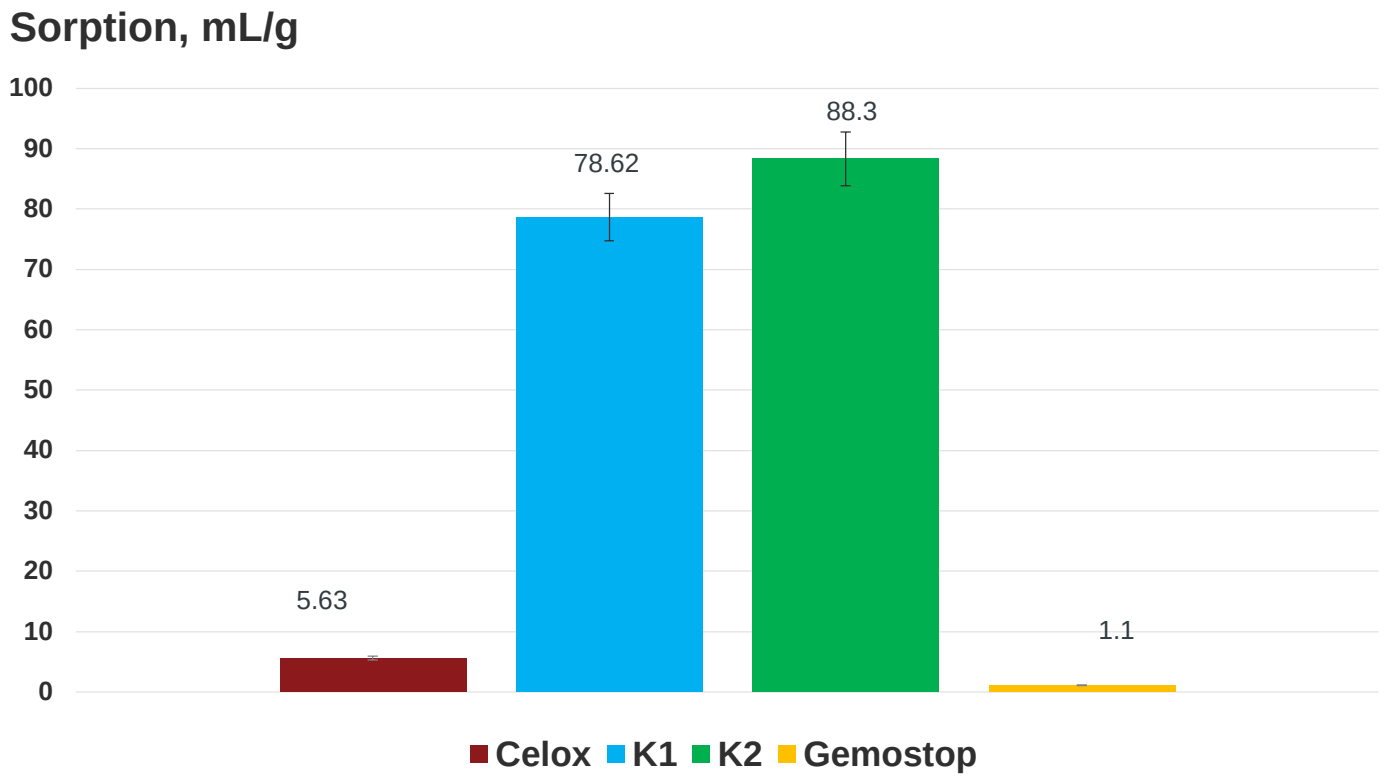
Effect "K1" and "K2" for the blood coagulation time in rabbits



n=10 in each group, P<0,05

The bleeding version of the drug K2 (3 min), K1 (8min) stopped the bleeding the fastest, especially compare to bleeding time with Celox (18 min) and Control groups (35 min).

Sorption rate "K1" and "K2"



n=10, P<0,05

The percentage of liquid absorption (1g of the agent absorbs 5.63g of water for the Celox). The largest volume of absorbed liquid per minute is observed in K1 (78.62 g) and K2 (88.3g), the smallest volume in the Gemostop (1.1 g) and the mean value of the Celox (5.63 g).

Experiments compositions "K1" and "K2"

- **Effects of Gemma compositions "K1" and "K2" on wound tissue regeneration**

Experiment was carried out on male white Vistar rats. 38 animals, which were pre-anesthetized, on the dorsal side of the body with artificial wounds size 3cm^2

The wound of first group K1 and second group K2 were applied (10 animals in each group). The third group (10 animals) wound was treated with “celox”.
The 4th group of 8 animals was the control group, and the wound were not treated.

- **Results:**

The wound which had been treated with the Gemma K2 were healed twice as fast, whereas the control sample Celox wound healing efficacy did not differ from control group.

Epithelization of wounds at K2 group was initiated on the second day after application of the composition. All data are statistically trustworthy.

Wound healing in rats influenced by compositions K2 and K1

Sample	n	Wound area* (S) during the observation period, см^2 (M±m)				
		1-3 day	3-6 day	6-9 day	9-11 day	11-13 day
K2 (Gemma 2)	10	4,0±0,7	1,1±0,4	0,2±0,1	-	-
K1 (Gemma 1)	10	4,2±0,9	2,0±0,4	0,7±0,2	0,4±0,1	-
Celox	10	4,1±1,0	3,2±0,3	2,4±0,3	1,0±0,3	0,3±0,1
Control	8	4,0±0,6	3,6±0,6	2,6±0,6	1,5±0,5	0,5±0,2

* P⩽0,05- As can be seen from table 1, in fact 2 times faster healing wounds in animals, the wound which had been treated with the K2- (6 to 13 days), whereas the control sample Celox efficiency did not differ from controls. Epithelization of wounds was initiated on the second day after application of the composition.

NOIGEL’s Binary hemostatic: Gemma

Advantages of Gemma over current hemostatic(s).

1. Has strong biocompatibility with body tissues, thereby not causing necrosis and allergic reactions.
2. Does not cause burns during crystallization in the wound.
3. Biodegradable and does not require removal from the wound.
4. Contains inexpensive raw materials based on natural semisynthetic polymers.
5. Absorbs 70 times the amount of blood than existing products.
6. Easy to manufacture and not affected by the process of sterilization.

Areas of use

- **NOIGEL created a new generation of hemostatic agent for use:**
  - By the military in battlefield situations
  - By hospitals and trauma centers who treat acute bleeding.
  - By surgeons to help stop bleeding during complex procedures.
  - In ambulances and other first responder situations.

Publications and IP for Hemostatic

IP:

1. Biologically active combinatorial derivatives of polysacharides. Inventors: Farber B., Farber S. Authors: Farber B., Farber S., Martynov A. PCT Application N. PCT/RU2017/000422
2. Pharmaceutical composition with hemostatic and regeneration actions. Inventors: Farber B., Farber S. Authors: Farber B., Farber S., Martynov A. PCT Application N. PCT/RU2014/000860
3. Farber, B.S., Martynov, A.V., & Kleyn, I.R. (2018). CREATION OF NEW MEDICAL DRUGS BASED ON TRIZ AND COMPUTER MATHEMATICAL MODELING. Annals of Mechnikov Institute, (4), 15–34. http://doi.org/10.5281/zenodo.2547580

Market Opportunity

$5.78bill

In 2016*

5.5%

CAGR period 2016-2022*

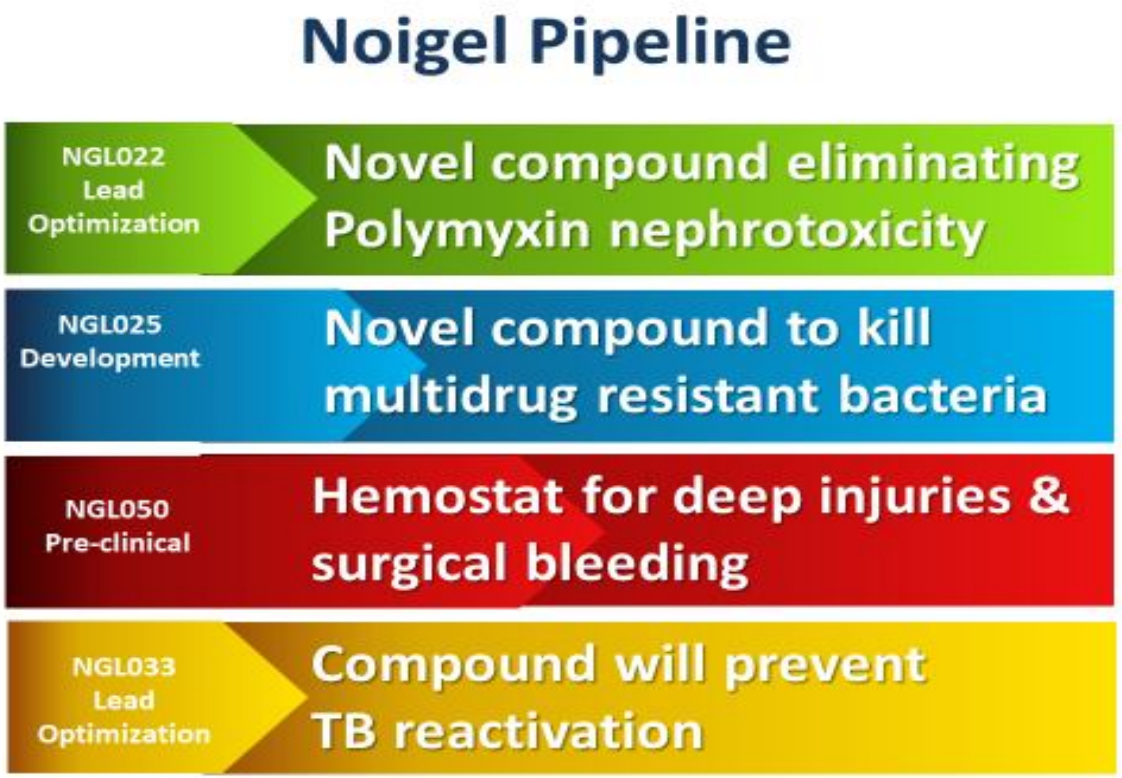
$7.98bill. USD

Will reach by 2022*

https://www.reuters.com/brandfeatures/venture-capital/article?id=11498 *
https://www.strategymrc.com/report/hemostasis-products-market

TRIZ method and ongoing pipelines

Company R&D snapshot



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