Blood as a Countermeasure for Radiation Injury

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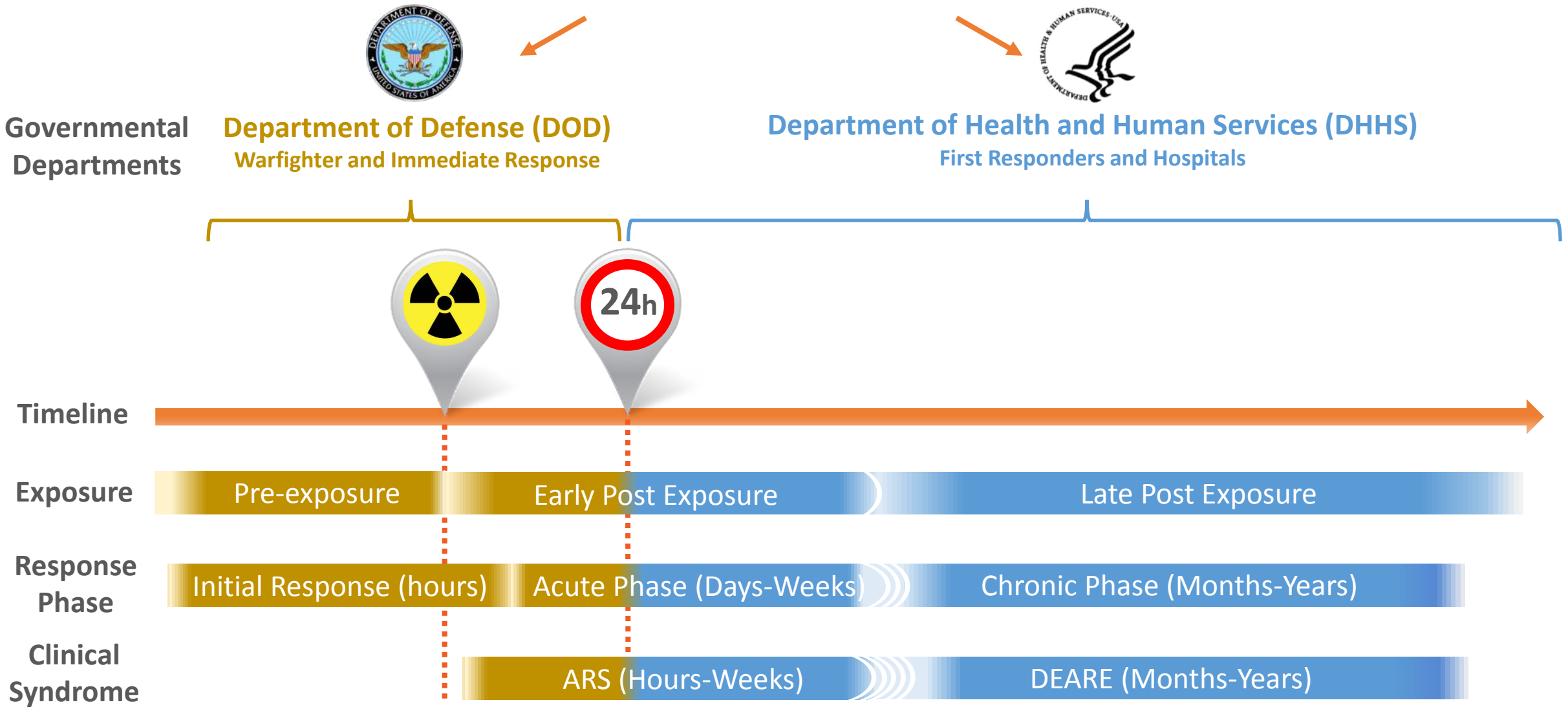
Blood

Countermeasures

Radiation Injury

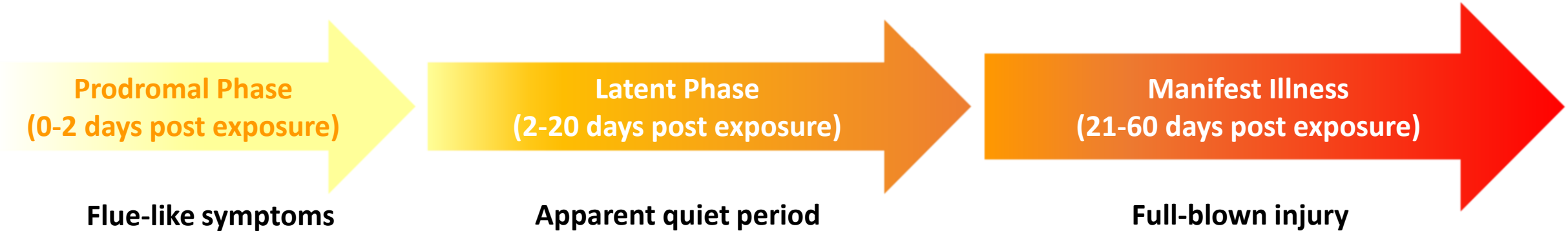
Timeline, Clinical Syndrome and Response ("U.S. Model")

Different Perspectives, Different Preparedness



Acute Radiation Syndrome (ARS)

- Acute exposure to high levels of radiation
- **Systemic in nature**
- Rapidly dividing cells are more sensitive (e.g. BM, GIT)
- Subsyndromes… (mainly for us… simplify triage, medical care and prognosis)

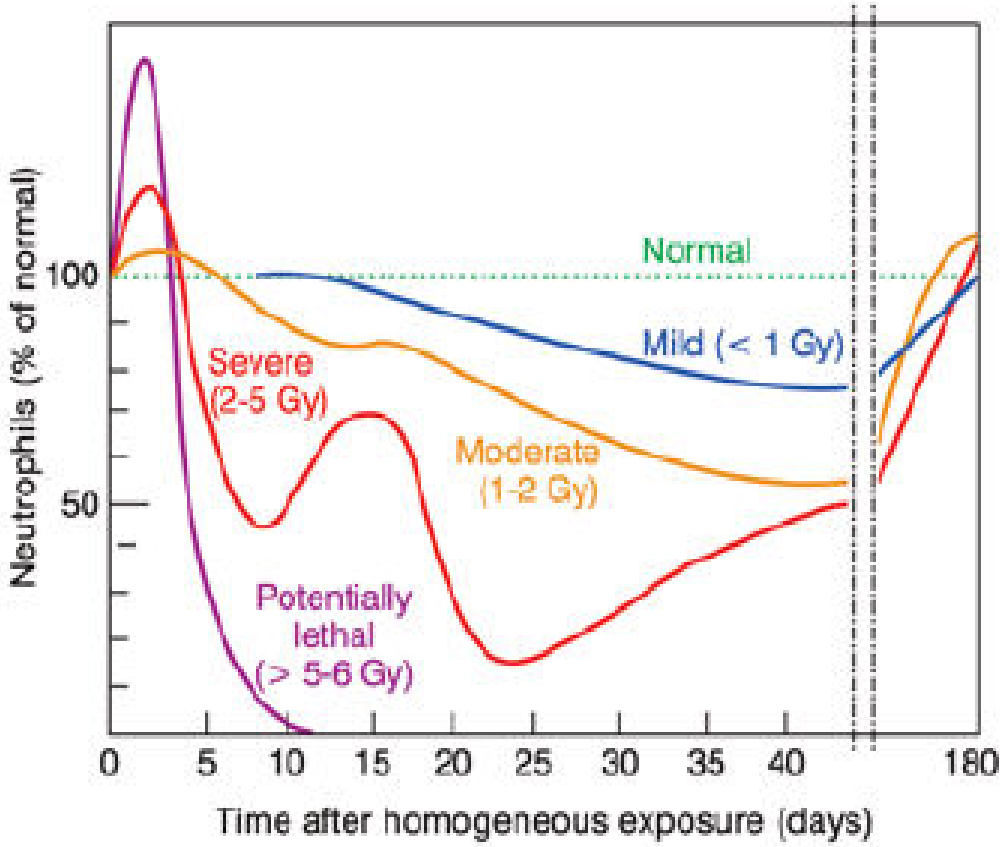


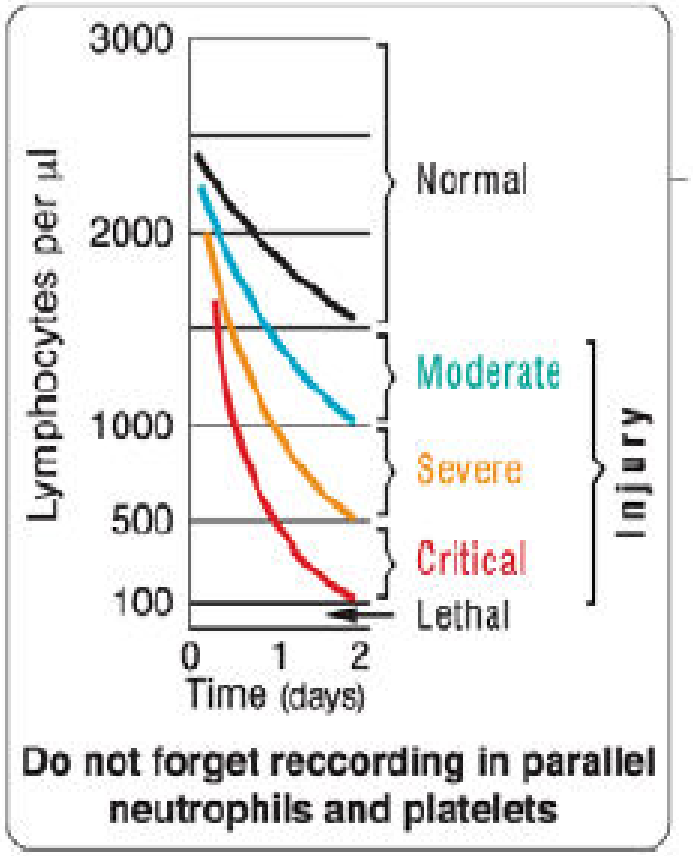
Acute Radiation Syndrome (ARS)

- Multi-Organ System Injury (=MODS/MOF)
- All systems are mostly hit at once
- Damage progresses variably in different organs/systems, and accumulates, depending on:
  - Type
  - Dose
  - Rate
  - TBI vs PBI

Tokaimura nuclear accident, Japan, 1999

ARS, BM Progenitor cells, and Blood Counts





= Anemia

Neutropenia

Thrombocytopenia

This could take time…

Blood Cell Depletion Curves
(https://www.remm.nlm.gov/rad_neutrophilcounts.htm)

Challenges of Treating Radiation Victims

- **Fears by health care providers**
- Like in any other mass casualty event = **limited resources**

  (physical damage d/t blast and shock wave, contamination, EMP, etc.)
- Emphasis on immediate needs for survival (e.g. antimicrobials, myelopoiesis)
- Injury to other organs (e.g. skin, lungs)
- Blood loss resulting from associated trauma and GI injury

ARS Management

- Early phase: efforts directed towards trauma, early initiation of cytokines, psychologic support
- Patients likely to manifest ARS and have the potential to survive should be identified and closely monitored (different approaches in different countries)
- Management of emesis, diarrhea, and (parenteral) nutrition
- Reverse isolation and dietary restrictions
- Prophylactic broad-spectrum antibiotics (infections and disruption of mucocutaneous barriers)

ARS Management

- Antifungal and anti-herpetic compounds are recommended
- Blood products should be administered “when necessary”, and with ARS = irradiated and leukoreduced
- Stem cell support relevant in severe cases
- All of that depends on repeated laboratory tests, another logistical-technical challenge of such an event
- Several weeks later – more victims with signs and symptoms which will need similar support

Highest Treatment Priorities for ARS Defined by U.S. DHHS

- Neutropenia
- Thrombocytopenia
- Vascular injury/sepsis
- Coagulopathy/hemostatic dysregulation
- Inflammation

Radiation Injury Target Areas Defined by U.S. DHHS

Trauma ⟷ Radiation

- Cell death/tissue repair & regeneration
- Inflammation/homeostasis
- Coagulopathy-fibrinolysis/hemostasis
- Ischemia/reperfusion
- Vascular injury/sepsis/tissue integrity & bacterial clearance

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Radiation Injury

Radiation Injury MCMs in the U.S. SNS

All are myeloid colony stimulating factors

1. Neupogen® (Amgen) – G-CSF
2. Neulasta® (Amgen) – PEGylated G-CSF
3. Leukine® (Sanofi >>> Partner Therapeutics, Inc.) – GM-CSF

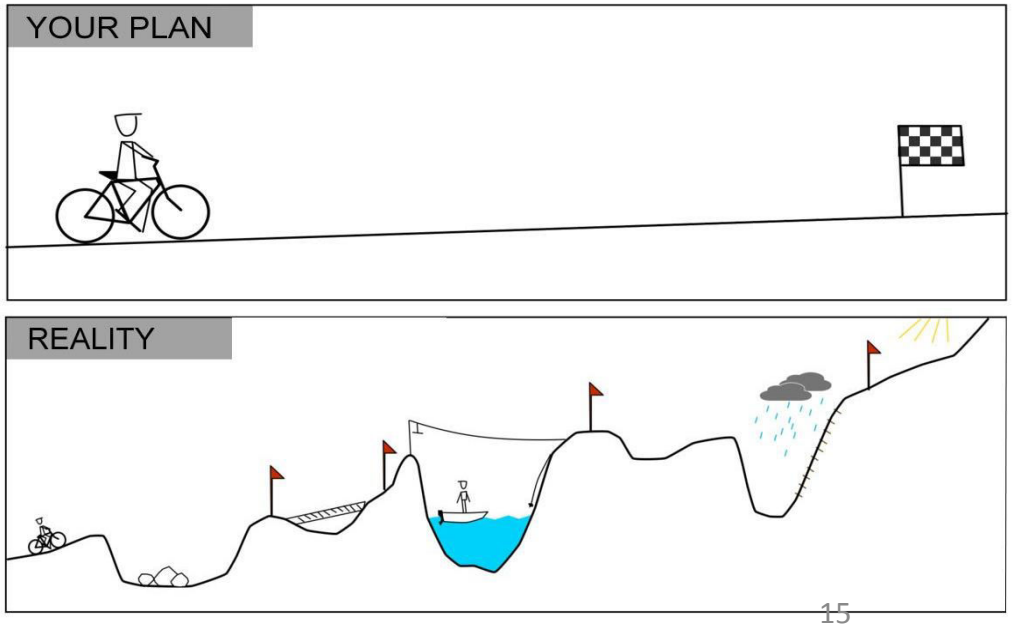
Radiation Injury MCMs in the U.S. SNS

The goals of using CSFs for radiation-induced myelosuppression are:

- Shorten the duration of severe neutropenia
- Minimize the severity of neutropenia-associated complications
- By that, improve survival of victims exposed to myelosuppressive doses

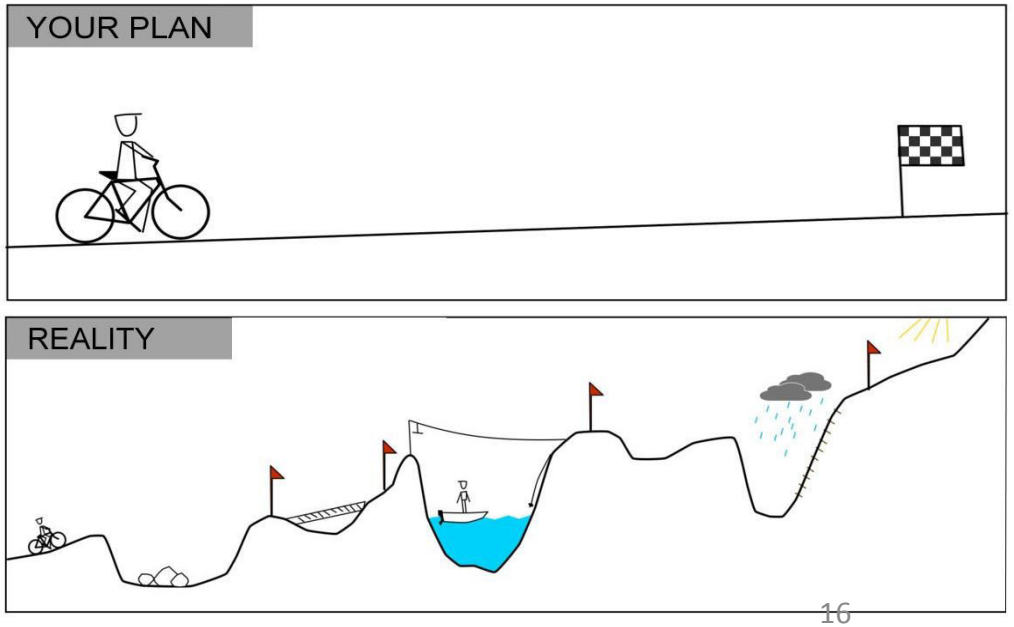
The “Ideal” MCM for Emergency Needs, including ARS

- Appropriate for a mass casualty scenario and a mass deployment setting
- To be effective and safe
- Oral dispensing is preferred
- Packaged for “unit of use”
- Licensed for specific indication



The "Ideal" MCM for Emergency Needs, including ARS

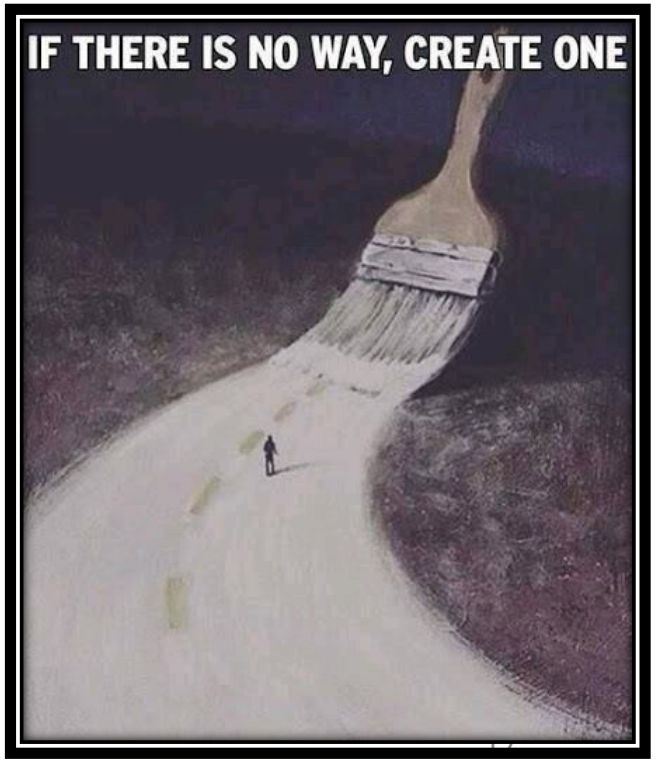
- Licensed for the entire population
- No need to monitor after dispensing
- No need for cold-chain management, mixing, or compounding
- Long, stable shelf life
- Inexpensive
- Easy for use, one time delivery



The “Ideal” MCM for Emergency Needs, including ARS

The Israeli approach:

- Changing/adding indications of currently used drugs
- Can I take it in my back-pack?
- Is it good against several agents?
- Out-of-the-box ideas…



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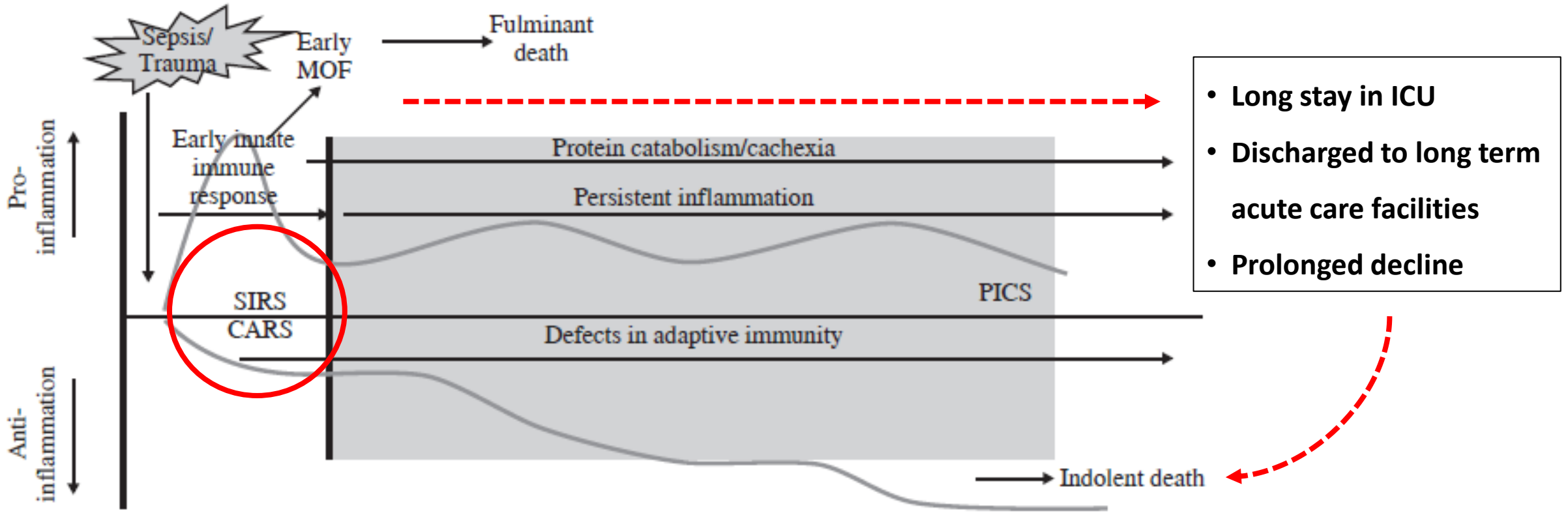
Blood

Countermeasures

Radiation Injury

Trauma/Tissue Injuries, Infection, Hypoxia, Hypotension



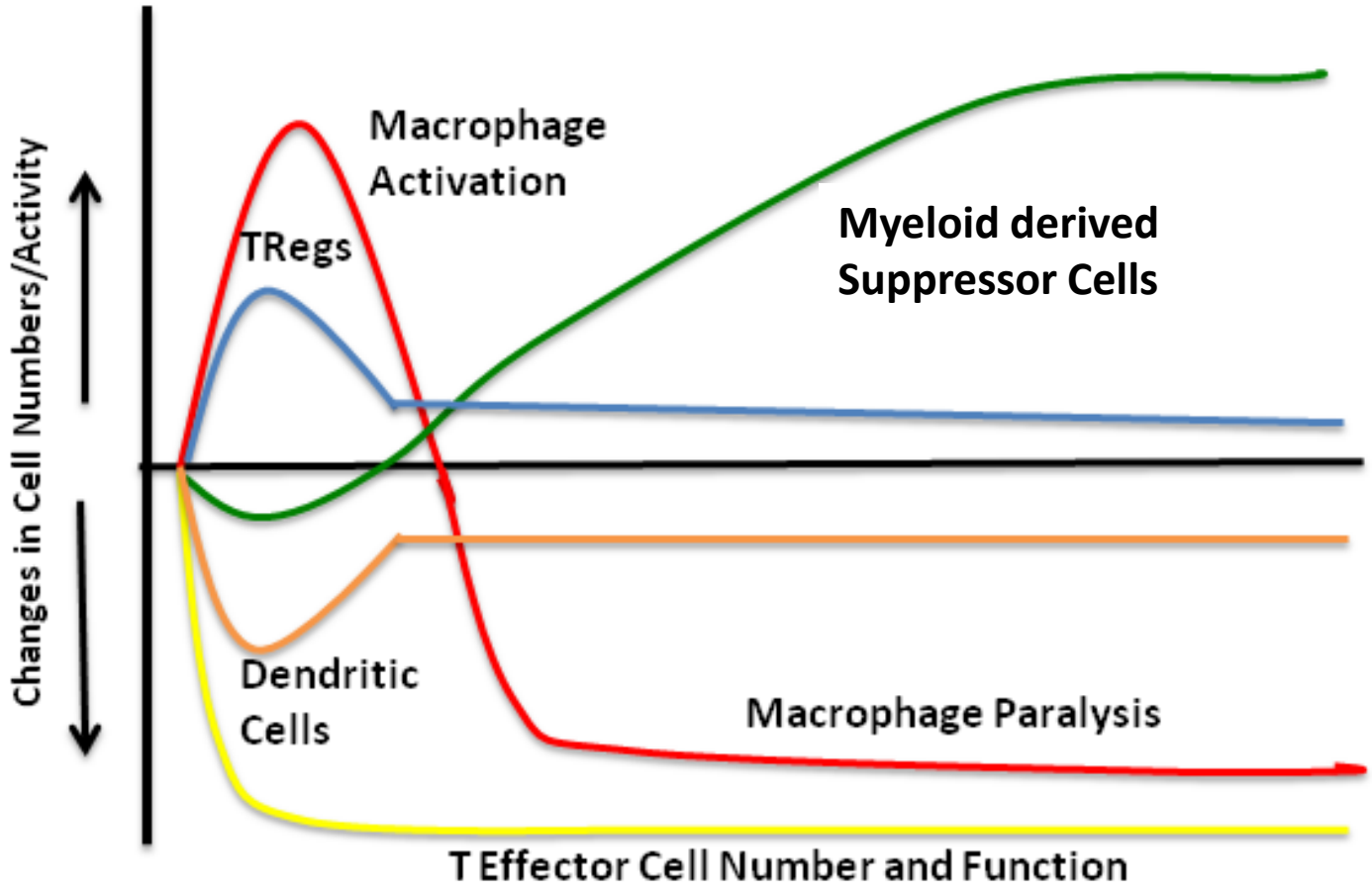
Early balance between the Systemic Inflammatory Response Syndrome and the Compensatory Anti-Inflammatory Response Syndrome

Trauma/Tissue Injuries, Infection, Hypoxia, Hypotension

Cell-Mediated Immune Response to Trauma + Radiation?

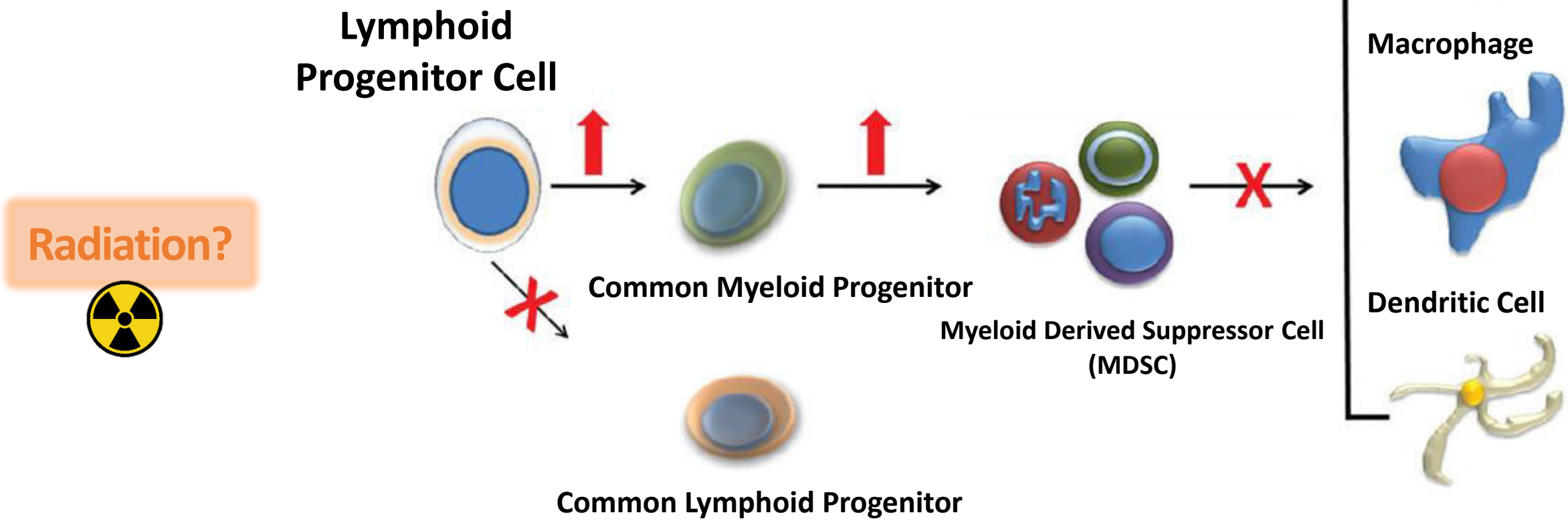
These patients suffer from:

- Ongoing protein catabolism
- Poor nutritional status
- Poor wound healing
- Recurrent infections
- Persistent low grade inflammation and…
- Defects in innate and adaptive immunity



Emergency myelopoiesis and expansion of the MDSC population

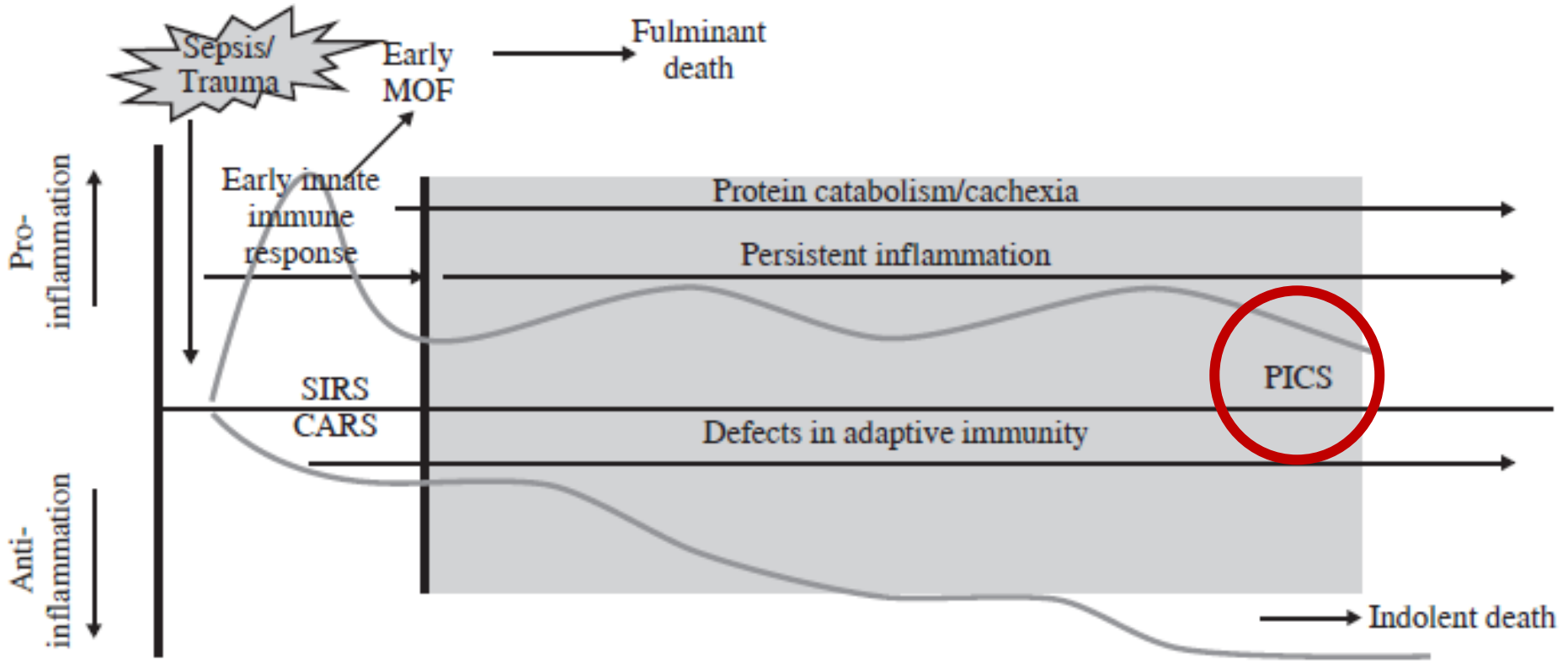
MDSC are expanded on the expense of lymphoid progenitors, leading to lymphopenia, and defects in maturation and differentiation of macrophages, neutrophils and dendritic cells



Trauma/Tissue Injuries, Infection, Hypoxia, Hypotension

Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS)

- ICU stay > 10 days
- Weight loss > 10%
- Increase CRP
- Low lymphocyte count
- Hypoalbuminemia



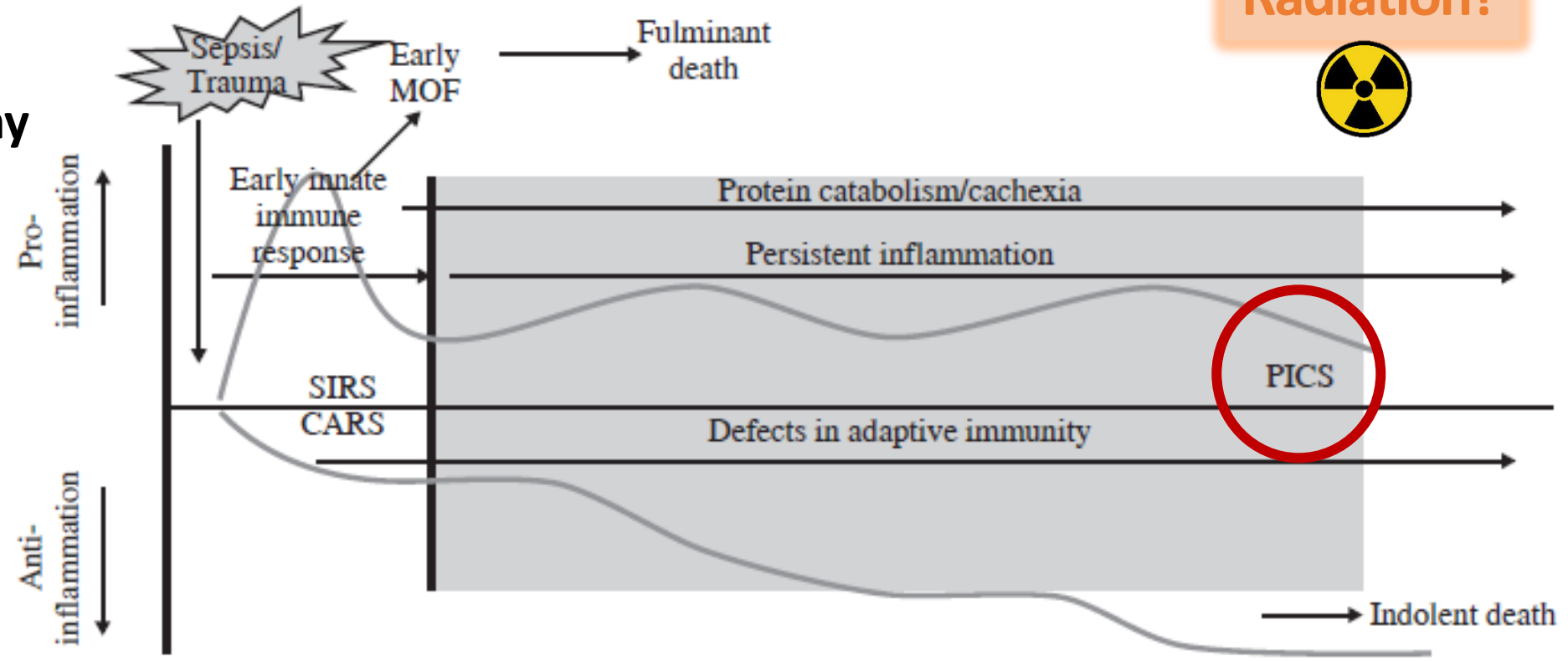
Trauma/Tissue Injuries, Infection, Hypoxia, Hypotension

Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS)

Secondary complications such as:

- **Respiratory failure**
- **Traumatic Coagulopathy**
- **Hypothermia**
- **Hypocalcemia**
- **Acidosis**
- **Infections**

Radiation?



- Trauma and radiation injuries have a lot in common, and in many of the victims – will be combined
- Blood products have an important role in the management of radiation victims, just as in trauma
- There are similar challenges when trying to use blood products

Can we really define blood products as MCMs?

I am not sure…

Challenges with Blood Products in RN Events

- Lack of sufficient blood products (early exhaustion, absence of basic supplies such as disposable collection packs)
- Might force compromising the routine (?)
- Contamination/infection
- The need for blood typing
- In ARS - external radiation and leukocyte reduction

Challenges with Blood Products in RN Events

- Blood transfusion services are energy-intensive
- Need for high-quality temperature control:
  - Refrigeration
  - Complex technical and computing demands
  - Transport/deployment (from donors to testing centers to hospitals)
- Short shelf-life (~30-40 days)
- Deployment to austere environments

Challenges with Blood Products in RN Events

- Near-by hospitals might be severely damaged
- Large numbers of medical staff killed/injured
- Clinical service might be non-existent

- Complete or near complete breakdown of the ability to provide safe blood products the way we are used to today

So – What is "the Key"?

- What is your assessment and prediction as to how many of each product we should keep?
- **Decision makers don't want to see the worst case scenario…**
- **They provide an X amount of money, and you have to get prepared…**

kept and prepared?

- Any risk-assessment performed lately…?

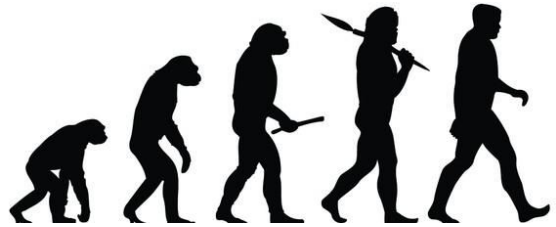
Potential Solutions for These Gaps

R&D efforts are primarily focused on:

- Deve onality (oxyg blood com
- Synt can be carri
- Platforms that inactivate a broad spectrum of pathogens as well as leukocytes

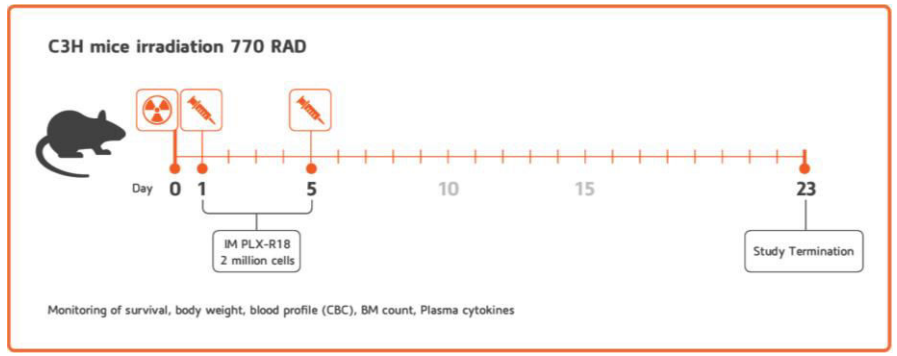
- **Testing these products for their beneficial effect in ARS models is imperative**
- **If successful, we might be able to define blood products as a real MCM against radiation injury**

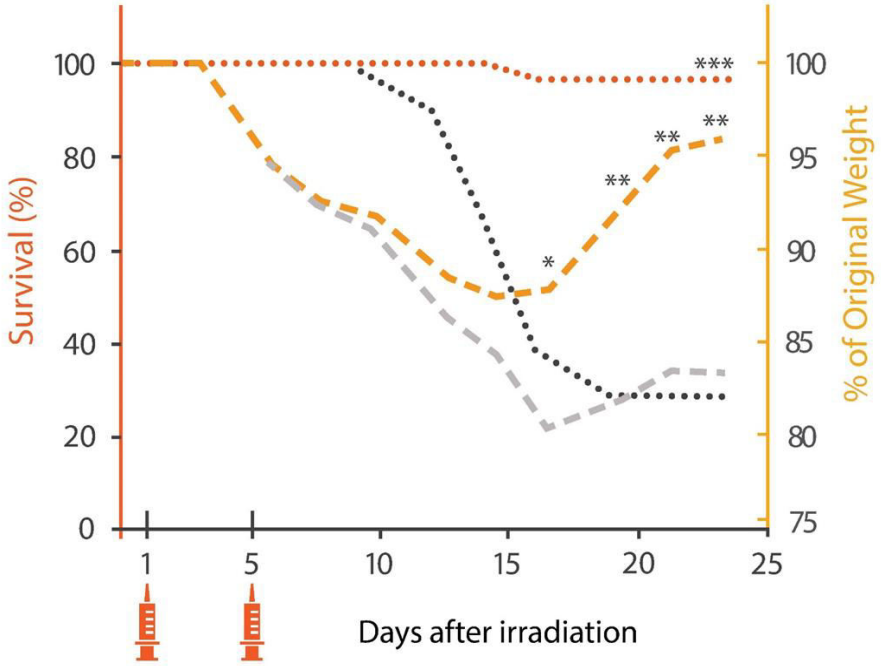
Out-of-the-Box Solutions



- Placenta expanded (PLX) stromal cells
- Two IM administrations
- The cells do not migrate or differentiate
- No need for blood typing or tissue matching
- More than 20,000 doses from one placenta
- Adaptive slow release secretion patterns based on signals
- Two phase 3 studies for other indications in Europe and the U.S.
- **IND for ARS cleared by the FDA**

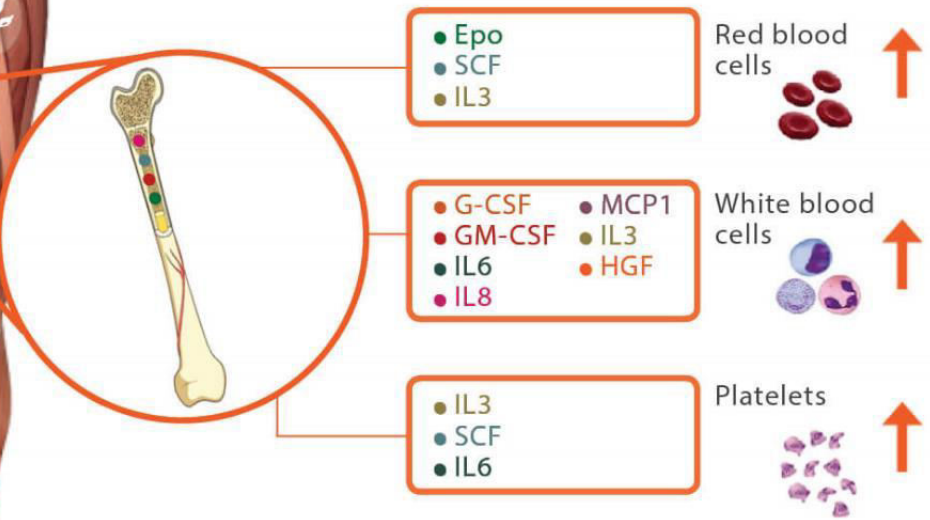
Out-of-the-Box Solutions

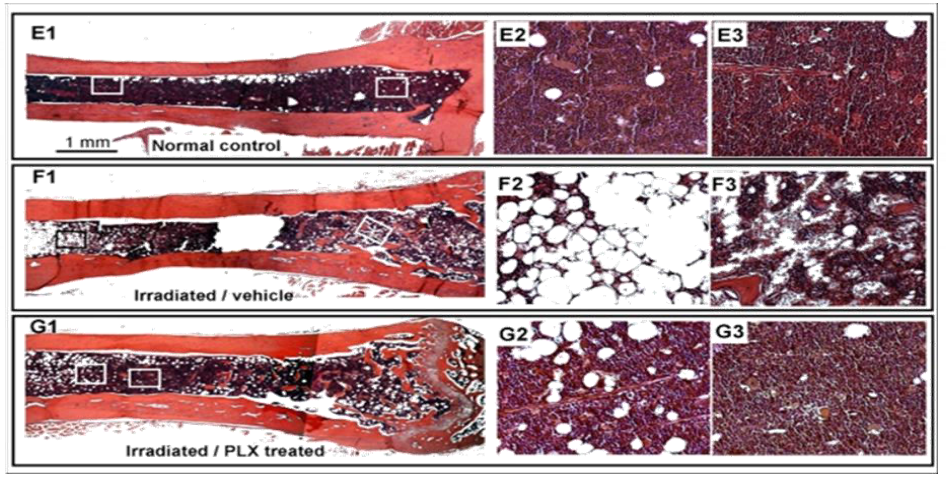




Body Weight:
- irradiated + vehicle
- irradiated + PLX-R18
- * p value < 0.01
- ** p value < 0.001

Survival Rate:
- irradiated + vehicle
- irradiated + PLX-R18
- *** p value < 0.0001



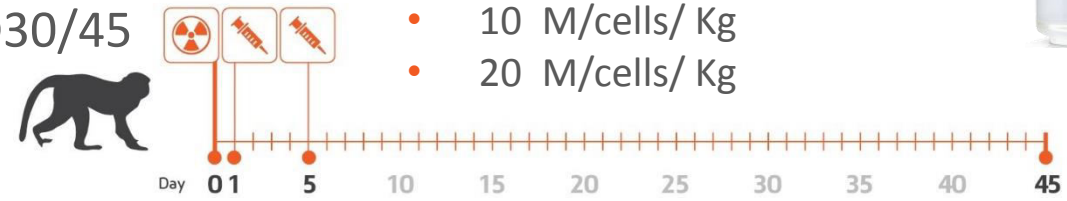


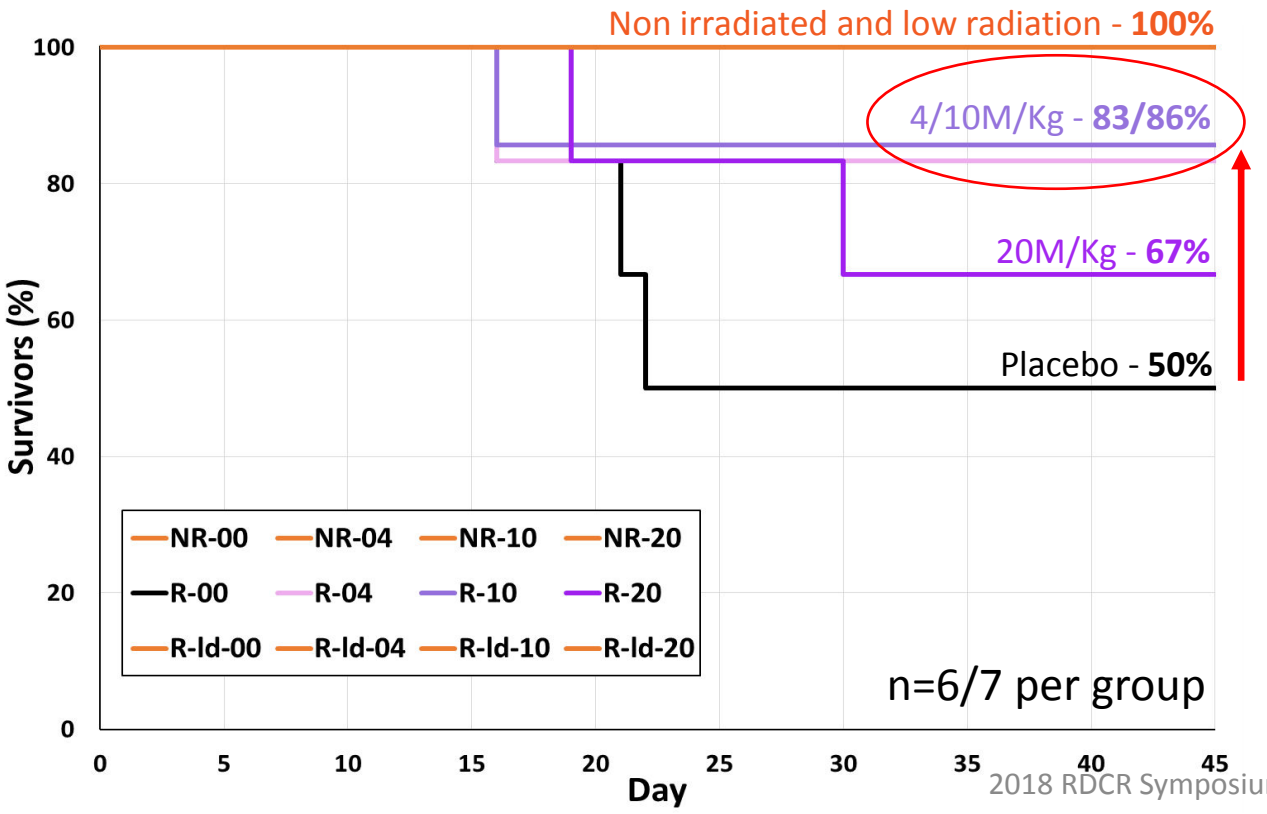
Out-of-the-Box Solutions

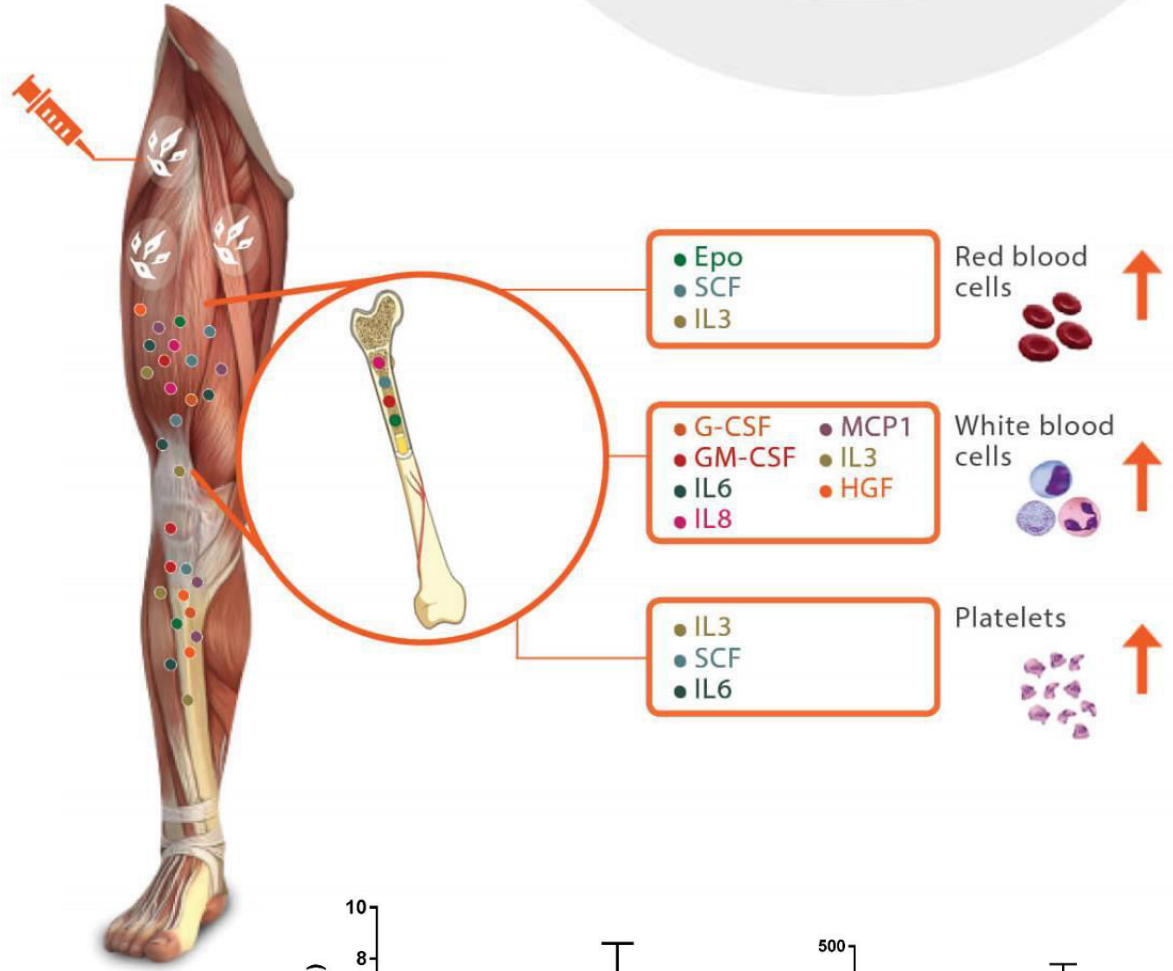
62 irradiated and non-irradiated Rhesus monkeys
Three cell doses:

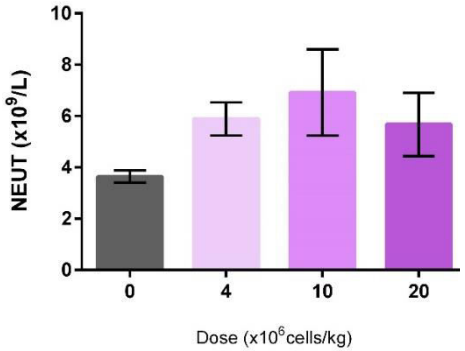
- 4 M/cells/ Kg
- 10 M/cells/ Kg
- 20 M/cells/ Kg

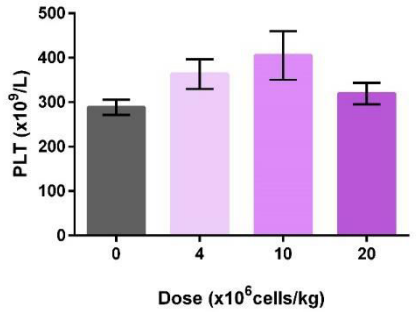
LD30/45











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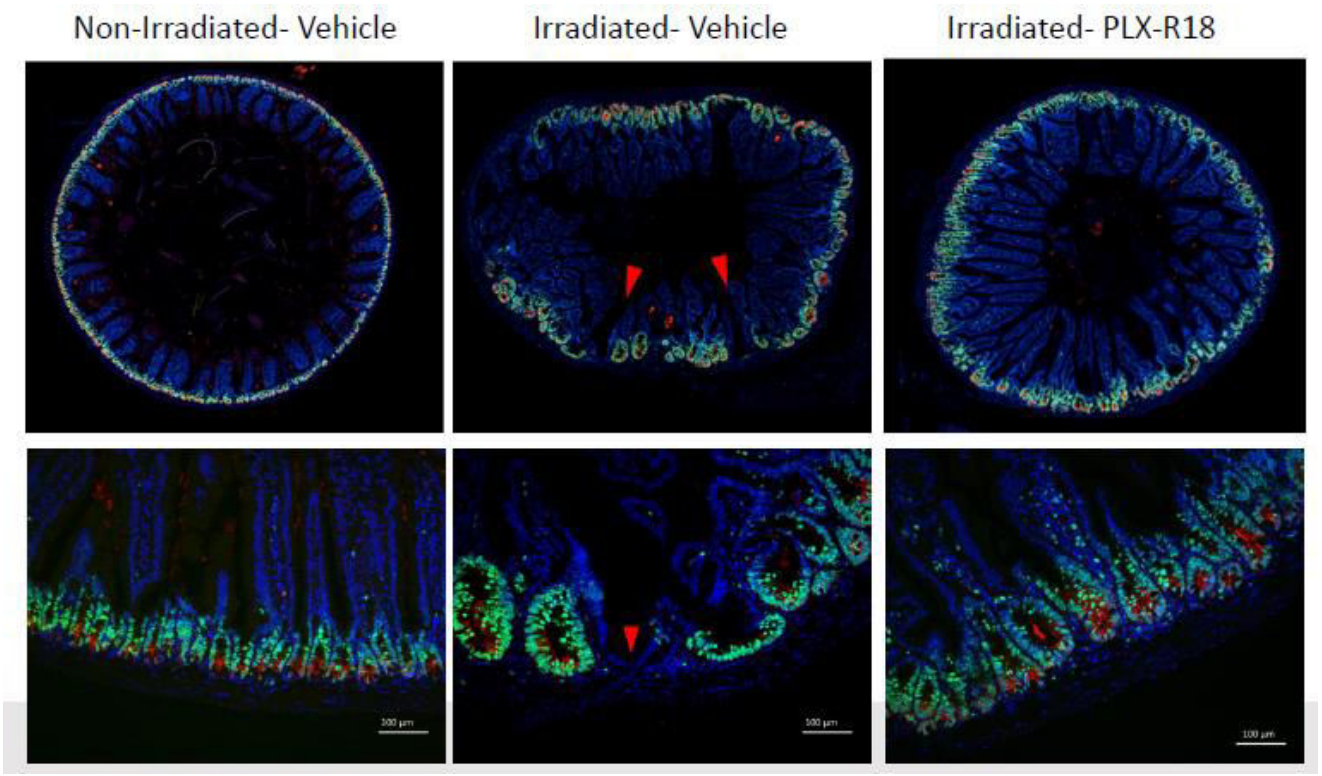
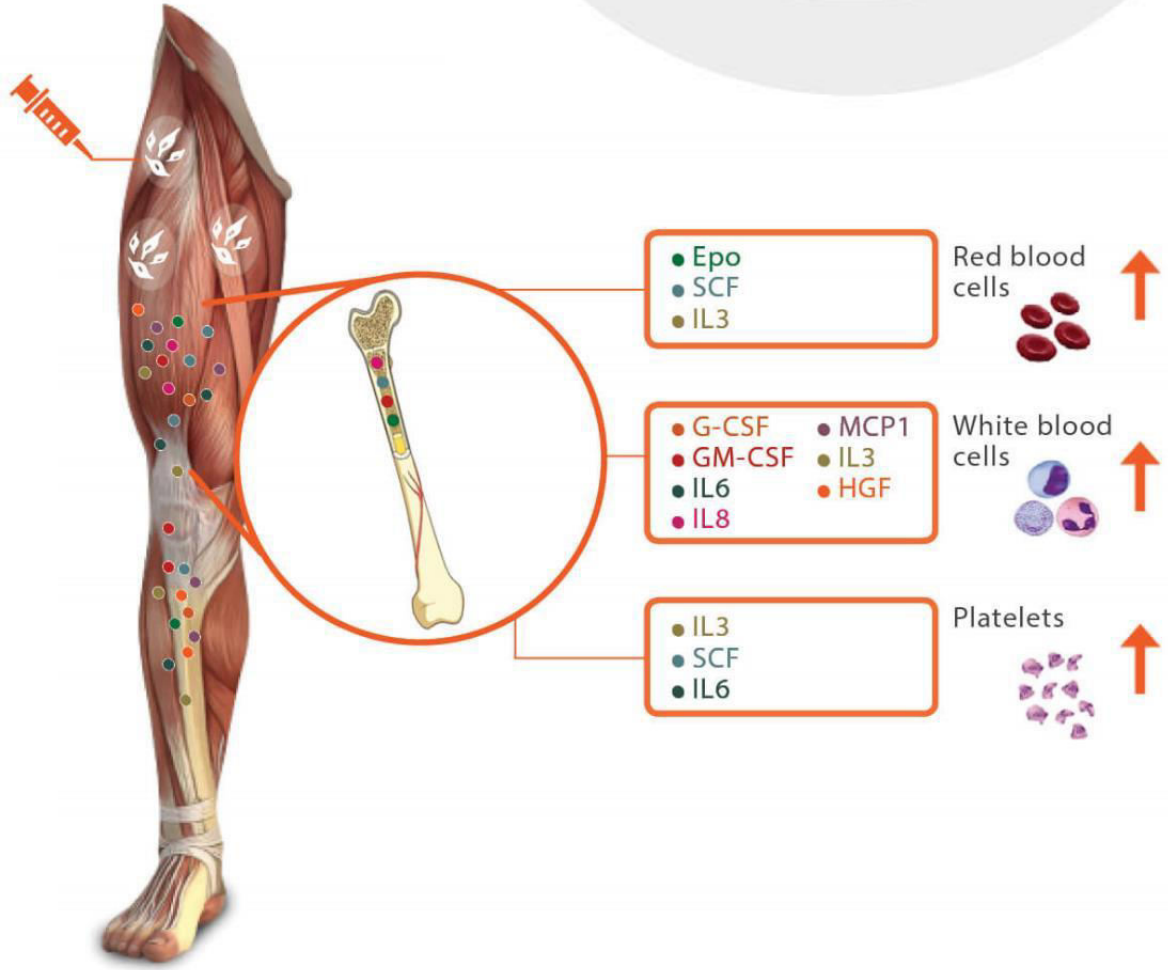




Out-of-the-Box Solutions

Mass production of PLX-R18 in cGMP facilities

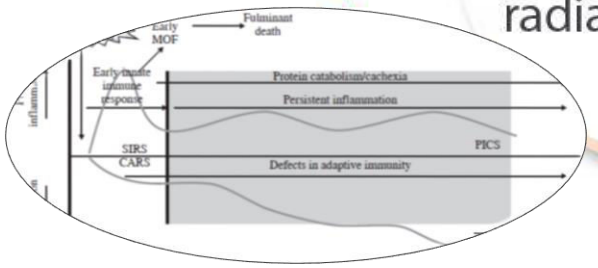
PLX-R18 stored ready to use

Radio-nuclear event

PLX-R18 deployed to disaster area

IM administration to affected population

Mitigation of radiation induced lethality



In Conclusion

- Blood products are relevant in radiation injury
- It’s Time to Bring the Trauma and the RN Teams Together…

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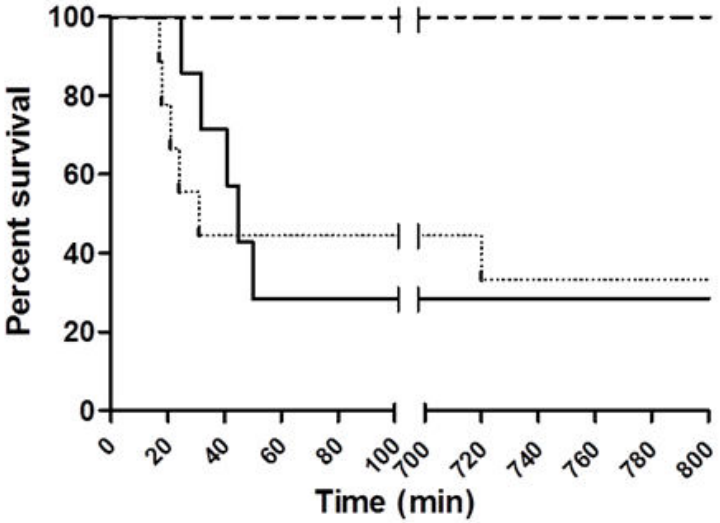
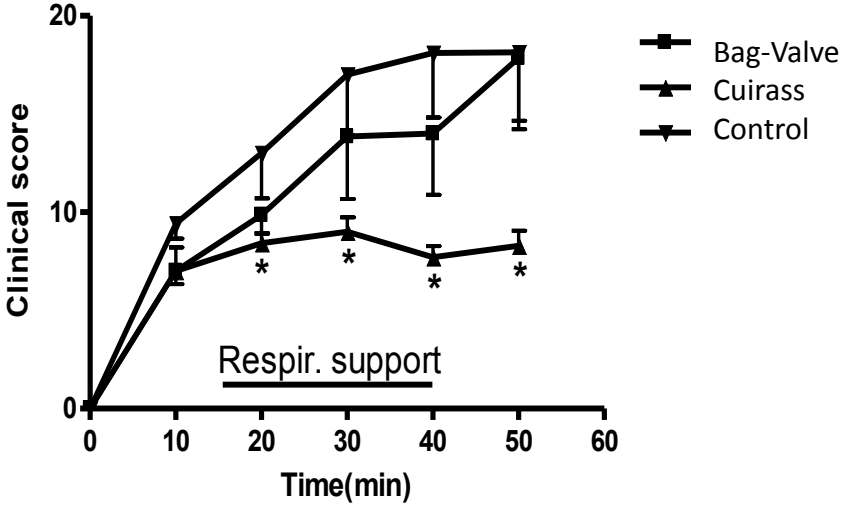
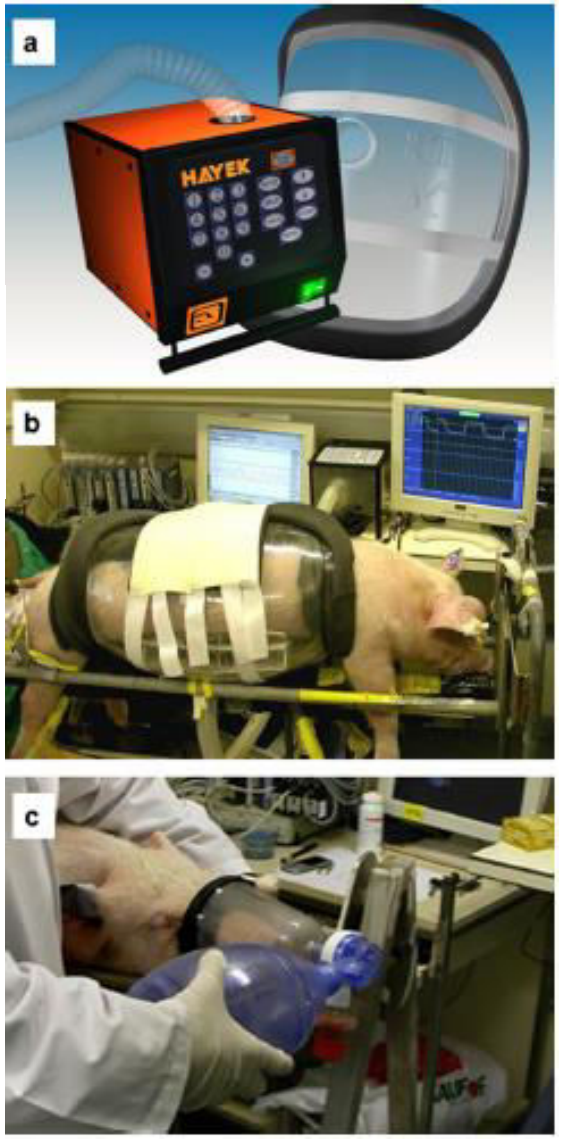
Biphasic cuirass ventilation is better than bag-valve mask ventilation for resuscitation following organophosphate poisoning

Ilan Gur[a], Shlomo Shapira[b], Shahaf Katalan[b], Amir Rosner[b], Shlomo Baranes[b], Ettie Grauer[b], Jacob Moran-Gilad[c], Arik Eisenkraft[c,d,e,*]



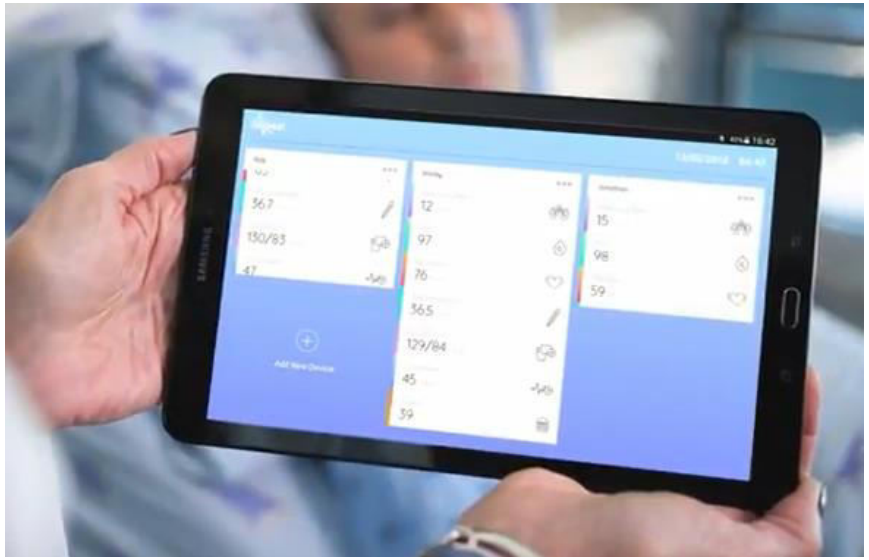


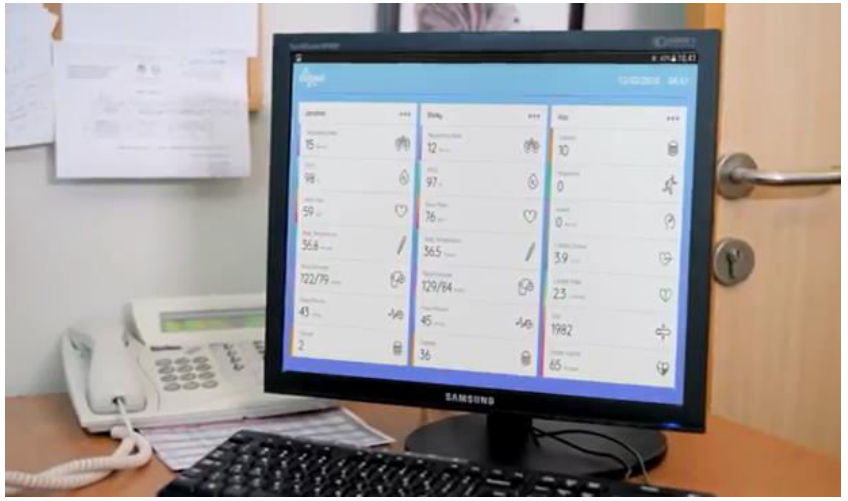
* p<0.02




Device Name
11/07/2017
70
3.4
3.5
1,100
60
3


Respiratory Rate
Saturation
Heart rate
Steps
Fall Alarm
Pulse pressure
Cardiac Output
Continuous Blood Pressure
Cardiac Index
Sweat
Heart Rate Variability
Systemic Vascular Resistance
Stroke Volume
Temperature



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