TURTLE HEALING BAND CLINIC

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INDIGENOUS MEDICINE
IMRB
INSTITUTIONAL REVIEW BOARD

INDIGENOUS MEDICINE DEFINITION

"Indigenous medicine (a.k.a. "traditional medicine") is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to native cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness ***including, but not limited to alternative, complementary, holistic, and integrative approaches***."

References

1. Declaration Recognizing the First Nation Medical Board (July 17, 2018).
2. U.S.C. Title 25, Section 1680u (2010).
3. "General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine," World Health Organization (2000).

IMIRB OBJECTIVES

The Indigenous Medicine Institutional Review Board ("IMIRB") will assist the First Nation Medical Board ("FNMB") and Crow Nation in defining, clarifying, and understanding the scope of practice for Indigenous Medicine ("IM"). The following objectives will be pursued:

- Guidelines for research submissions will be established;
- ***Applications will be accepted only from FNMB licensees***;
- Safety and efficacy of IM diagnostic devices, substances, and modalities will be assessed;
- Availability of IM therapies will be published;
- Clinical outcomes of IM research studies will be reviewed;
- Social impact of IM research studies will be evaluated;
- Economic impact of IM research studies will be studied; and
- Means for developing an integrative relationship between IM and other healthcare concepts will be explored.

IMIRB RESULTS

Indian Tribes and THB Members will have access to medical alternative devices, therapies, and substances that might otherwise be unavailable. As information becomes available, tribal providers will better understand IM from ***non-interventional studies*** conducted under IMIRB jurisdiction. Industries supporting IM may seek to affiliate with IMIRB and establish facilities on Indian Lands/Indian Land Trusts thereby increasing employment for Indian Tribe(s).

NON-INTERVENTIONAL IRB

Interventional IRB

"A clinical study in which ***participants are assigned to groups that receive one or more intervention/treatment (or no intervention)*** so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions."

Non-Interventional IRB

"A clinical study in which ***participants receive one intervention/treatment used in a provider's practice that is already known to be safe***. Participants are not assigned to multiple groups, but rather receive one standard protocol where selected measurements (e.g., biomarkers) are monitored in a prospective manner as part of the provider's routine practice. No new drug or new device approval is being sought from U.S. FDA."

IRB PHASE 1 vs PHASE 2

Phase 1

A phase of research to describe clinical trials that ***focus on the safety of a drug***. They are usually conducted with healthy volunteers, and the goal is to determine the drug's most frequent and serious adverse events and, often, how the drug is broken down and excreted by the body. These trials usually involve a small number of participants (e.g., 20 to 80).

Phase 2

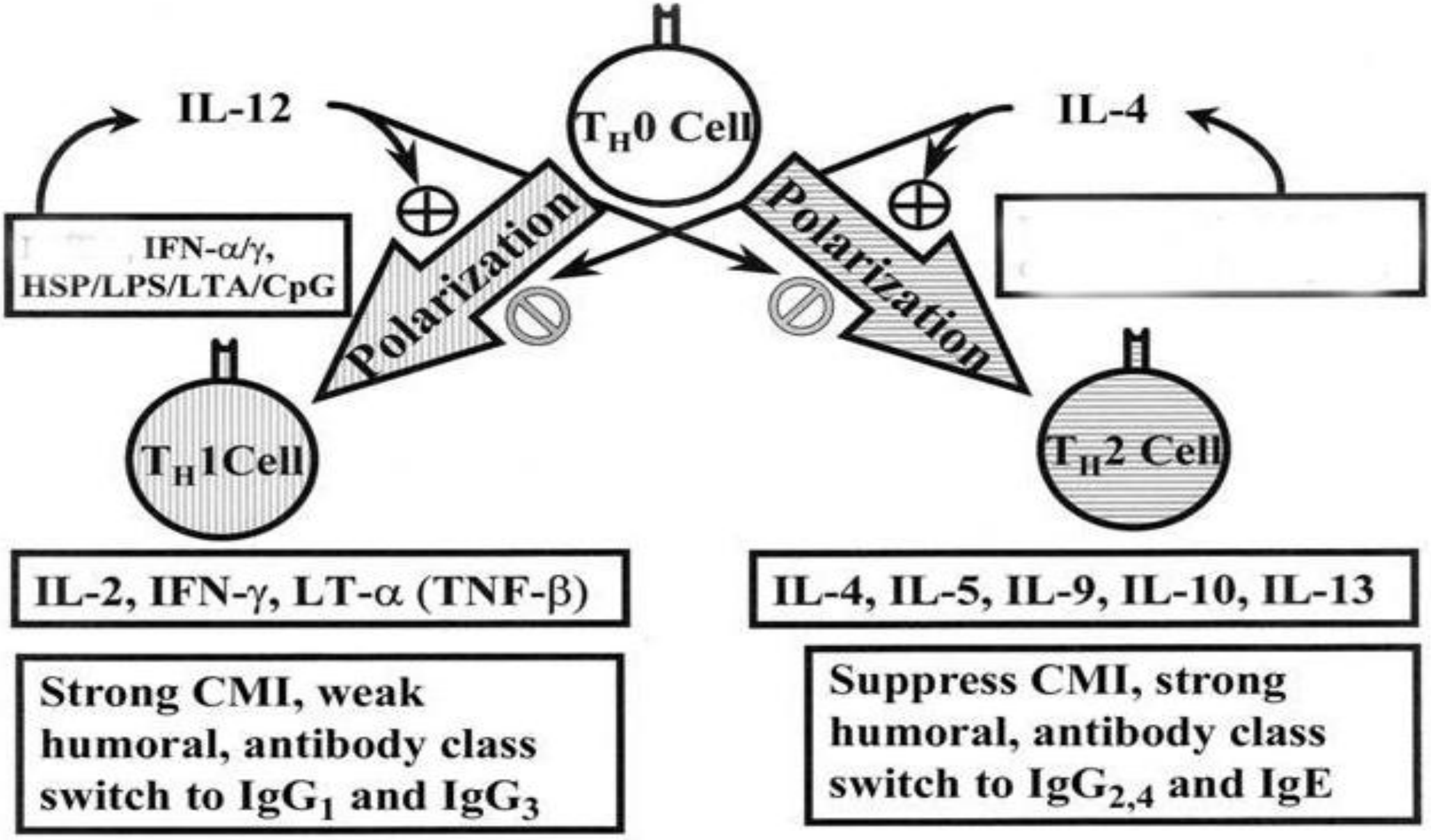
A phase of research to describe clinical trials that gather preliminary data on whether a drug works in people who have a certain condition/disease (i.e., the drug's effectiveness). For example, ***participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug***. These trials involve 100’s of participants and can last for several years.

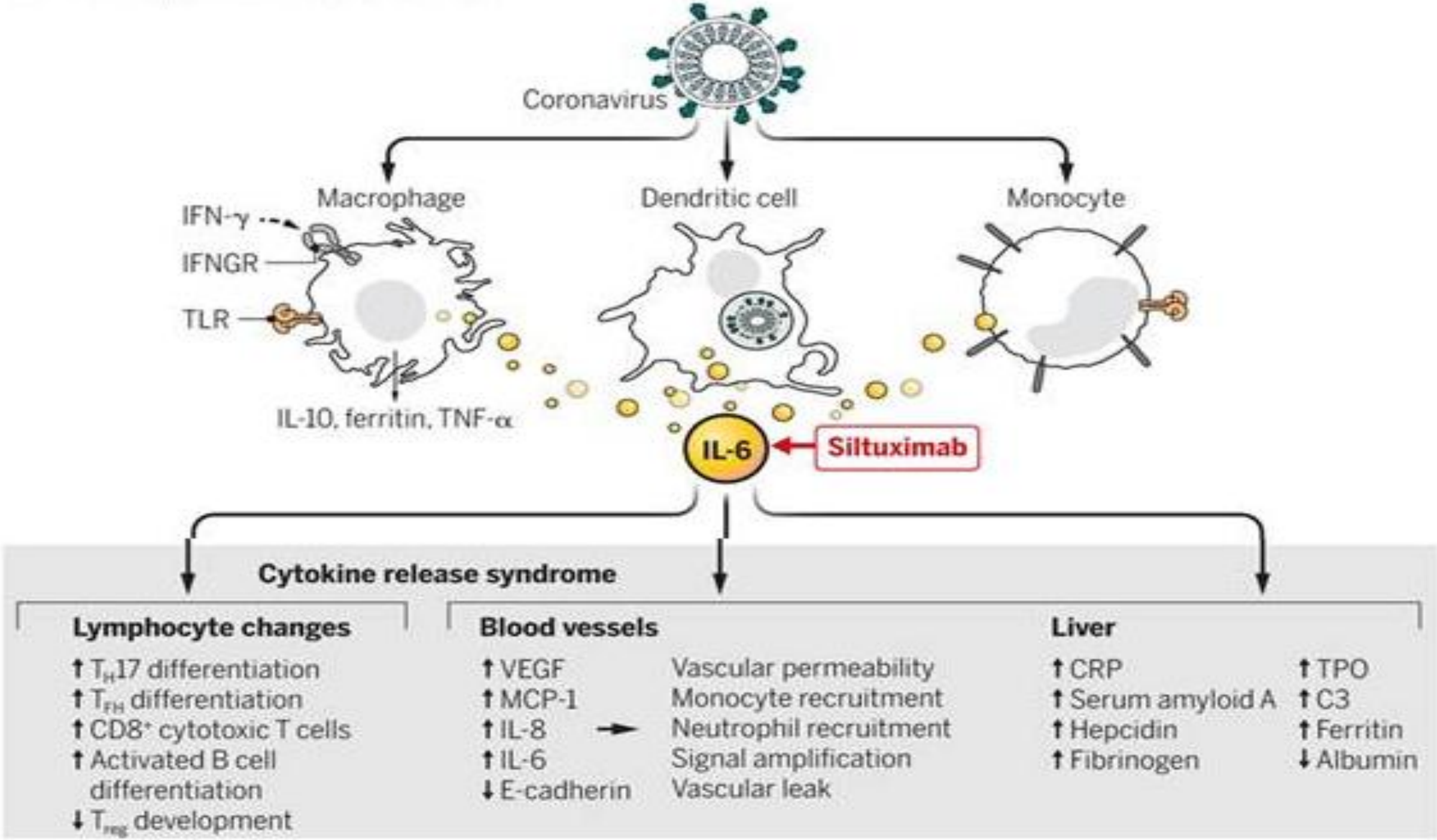
APPLICABLE CLINICAL TRIAL ("ACT")

Questions

1. **Is the study interventional (a clinical trial)?**
2. **Do ANY of the following apply:**
   a. **Is at least one study facility located in the United States or a U.S. Territory?**
   b. **Is the study conducted under a U.S. FDA Investigational New Drug application (IND) OR Investigational Device Exemption (IDE)?**
   c. **Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country?**
3. **Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)?**
4. **Is the study other than a Phase 1 trial of a drug and/or biological product or is the study other than a device feasibility study?**

If "Yes" is answered to all 4 questions, and the study was initiated on or after January 18, 2017, the trial would meet the definition of an ACT that is required to be registered under 42 CFR 11.22 with ClinicalTrials.gov.


IL-12
T_H0 Cell
IL-4
IFN-α/γ,
HSP/LPS/LTA/CpG
Polarization
Polarization
T_H1Cell
T_H2 Cell
IL-2, IFN-γ, LT-α (TNF-β)
IL-4, IL-5, IL-9, IL-10, IL-13
Strong CMI, weak humoral, antibody class switch to IgG_1 and IgG_3
Suppress CMI, strong humoral, antibody class switch to $IgG_{2,4}$ and IgE


Coronavirus
Macrophage
Dendritic cell
Monocyte
IFN-γ
IFNGR
TLR
IL-10, ferritin, TNF-α
IL-6
Siltuximab
Cytokine release syndrome
Lymphocyte changes
↑ T_H17 differentiation
↑ T_{FH} differentiation
↑ $CD8^+$ cytotoxic T cells
↑ Activated B cell differentiation
↓ T_{reg} development
Blood vessels
↑ VEGF
↑ MCP-1
↑ IL-8
↑ IL-6
↓ E-cadherin
Vascular permeability
Monocyte recruitment
Neutrophil recruitment
Signal amplification
Vascular leak
Liver
↑ CRP
↑ Serum amyloid A
↑ Hepcidin
↑ Fibrinogen
↑ TPO
↑ C3
↑ Ferritin
↓ Albumin

SARS-CoV VACCINE

"Immunication with SARS Coronavirus Vaccines Leads to Pulmonary Immunopathology on Challenge with the SARS Virus," (Chien-Te Tseng et al., PLoS ONE, Vol. 7, Issue 4, April 20, 2012)

- Four candidate vaccines with and without alum adjuvant given to mice.
- All vaccines induced serum neutralizing antibody.
- All mice exhibited histopathologic changes in lungs two days after challenge to SARS-CoV.
- Histopathology was uniformly a Th2-type response with prominent eosinophil infiltration.
- Pathologic changes seen in all control groups lacked the eosinophil prominence.

CONCLUSION: Use caution in proceeding to application of a SARS-CoV vaccine in humans.

SARS-CoV-2 VACCINE

- **$1.2 Billion given to Oxford University from U.S.:**
  - ❖All of the monkeys exposed to SARS-CoV-2 and treated with "ChAdOx1" became infected and infected other monkeys. (www.TrialSiteNews.com, May 22, 2020).
- **$1.8 Billion given to Novavax from U.S.:**
  - ❖Vaccine contains patented saponin-based "Matrix-M." (ir.Novavax.org, July 7, 2020).
- **FDA says that vaccines should reduce COVID-19 rate by 50% and "the data should suggest it's highly unlikely that the vaccine could possibly be less than 30% effective."**
  - ❖"Experts see a chance for a COVID-19 vaccine this fall—if it's done right," (www.StatNews.com, September 2, 2020).

DENGVAXIA

- **2014**—Sanofi completes phase III testing for Dengvaxia in Philippines.
- **2016**—Philippines is 1st to receive live attenuated tetravalent Degnvaxia.
- **2017**—Sanofi issues statement on November 29th that Degnvaxia poses risk to individuals who have not been exposed to dengue fever.
- **2018**—Philippines files a lawsuit vs Sanofi for Dengvaxia deaths in children.
- **2018**—Europe approves Dengvaxia in December.
- **2019**—Philippines FDA revokes Sanofi license in February.
- **2019**—Philippines Department of Health rejects Sanofi's appeal in August.
- **2019**—FDA approves Dengvaxia for use in United States on May 1st.
- **2020**—Philippines files criminal charges vs Sanofi President in February for >600 deaths (mostly children).

Conventional vaccines

- Weakened virus

- Inactivated virus

- Part of virus (antigen)

Antigen

RNA vaccines

mRNA
(messenger RNA)

DENDRITIC CELL VACCINE

1. Isolating DC's from blood of a healthy individual.

2. Exposing DC's to SARS-CoV2 antigen(s) in vitro.

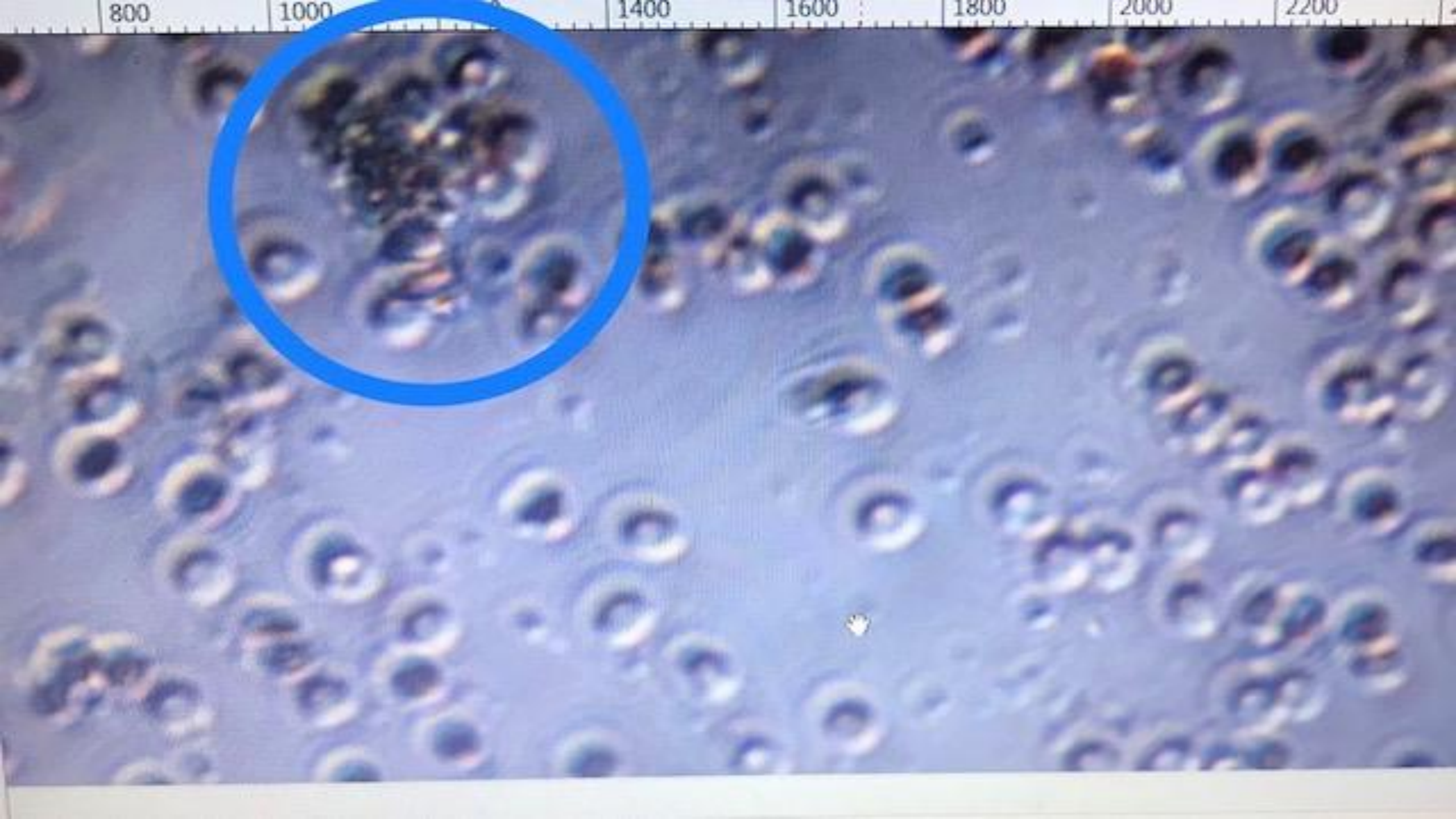
3. Maturing and stabilizing the DC's in vitro to engender a TH1-type immune response.

4. Reinjecting the antigen pulsed mature DS's into healthy individual to induce a TH1 response.

DENDRITIC CELL VACCINE PROTOCOL

1. Patient is seen and evaluated by a THBC Tribal Provider.
2. Patient has blood draw to test SARS-CoV2 antibody level(s).
3. Patient donates blood.
4. Dendritic Cells are harvested from blood.
5. Dendritic Cells are exposed to SARS-CoV-2 Antigen for 3-5 days.
6. Dendritic Cells are returned to the patient via IVP and/or lymph node injections 5-7 days after blood draw.
7. Patient has blood drawn in 2, 4, and/or 6 weeks for COVID-19 antibody level(s).
8. Patient may be given a follow-up booster dose injection to test the immune system’s memory response.

		NCT number	Indication	Interventions	Phase	Enrollment	Start date	Estimated primary completion date
Tumor lysate	1	NCT00703105	Ovarian cancer	Ontak (anti-CD25)|DC vaccine + ontak	Phase 2	36	2008	2018
	2	NCT01204684	Glioma|Astrocytoma|Astro-oligodendroglioma|Glioblastoma	Autologous tumor lysate-pulsed DC + 0.2% resiquimod|DC vaccination + polyICLC	Phase 2	60	2010	2018
	3	NCT01635283	Newly diagnosed or recurrent low-grade glioma	Tumor lysate-pulsed autologous DC vaccine	Phase 2	18	2012	2019
	4	NCT01946373	Malignant melanoma	Cyclophosphamide|Fludarabine|T cells|Interleukin-2|DC vaccine	Phase 1	10	2013	2018
	5	NCT01973322	Malignant melanoma stage III|Stage IV	Arm 1: autologous DC loaded with autologous tu lysate (DC vaccine) + RT|Arm 2: DC vaccine + IFN-α|Arm 3: both arm 1 and 2 + RT|Arm 4: DC vaccine	Phase 2	24	2013	2019
	6	NCT01957956	Newly diagnosed glioblastoma	Tumor lysate-pulsed autologous dendritic cell vaccine + temozolomide	Early phase 1	21	2013	2016
	7	NCT01808820	Malignant glioma|Glioblastoma	Dendritic cell vaccine|Tumor lysate|Imiquimod|Leukapheresis	Phase 1	20	2013	2019
	8	NCT02496520	Advanced solid tumors, sarcoma|Central nervous system tumor	Dendritic cells|Surgery as needed|Chemotherapy as needed|Radiation: radiation therapy as needed	Phase 1|2	10	2014	2018
	9	NCT01803152	Sarcoma|Soft tissue sarcoma|Bone sarcoma	Biological: dendritic cells vaccine|Lysate of tumor|Gemcitabine|Imiquimod|Leukapheresis	Phase 1	56	2014	2019
	10	NCT02718391	Malignant melanoma	DC pulsed with autologous tumor lysate	Phase 2	120	2015	2019
	11	NCT02301611	Malignant melanoma	Autologous Tumor Lysate (TL) + Yeast Cell Wall Particles (YCWP) + Dendritic Cells (DC) (TLPLDC Vaccine)|Placebo	Phase 2	120	2015	2019
	12	NCT02503150	Metastatic colorectal cancer	Antigen pulsed dendritic cells + chemotherapy|Chemotherapy	Phase 3	480	2015	2019
	13	NCT02678741	Metastatic melanoma	TLPLDC vaccine in addition to standard of care checkpoint inhibitor of choice	Phase 1|Phase 2	45	2016	2019
	14	NCT03395587	Newly diagnosed glioblastoma	Autologous DC pulsed with autologous tumor lysate	Phase 2	136	2018	2022
	15	NCT03360708	Recurrent glioblastoma	Cytokine-induced killer cells|Tumor lysate-pulsed autologous DC vaccine	Early phase 1	20	2018	2022
	16	NCT03014804	Recurrent glioblastoma	Autologous dendritic cells pulsed with tumor lysate|Nivolumab	Phase 2	30	2018	2020
RNA	17	NCT01983748	Uveal melanoma	Autologous DC loaded with autologous tumor RNA	Phase 3	200	2014	2022
Peptide	18	NCT02775292	Adult solid neoplasm|Childhood solid neoplasm|Metastatic neoplasm	Aldesleukin|Cyclophosphamide|Fludarabine phosphate|Nivolumab|NY-ESO-1 reactive TCR retroviral vector transduced autologous PBL|NY-ESO-1(157-165) peptide-pulsed autologous DC vaccine	Phase 1	12	2017	2019
Tumor neoantigen	19	NCT01885702	Colorectal cancer	Neoantigen-loaded DC vaccination	Phase 1|2	25	2010	2016
	20	NCT03300843	Melanoma|Gastrointestinal|Breast|Ovarian|Pancreatic cancer	DC vaccine loaded with neoantigen coding peptide	Phase 2	86	2018	2027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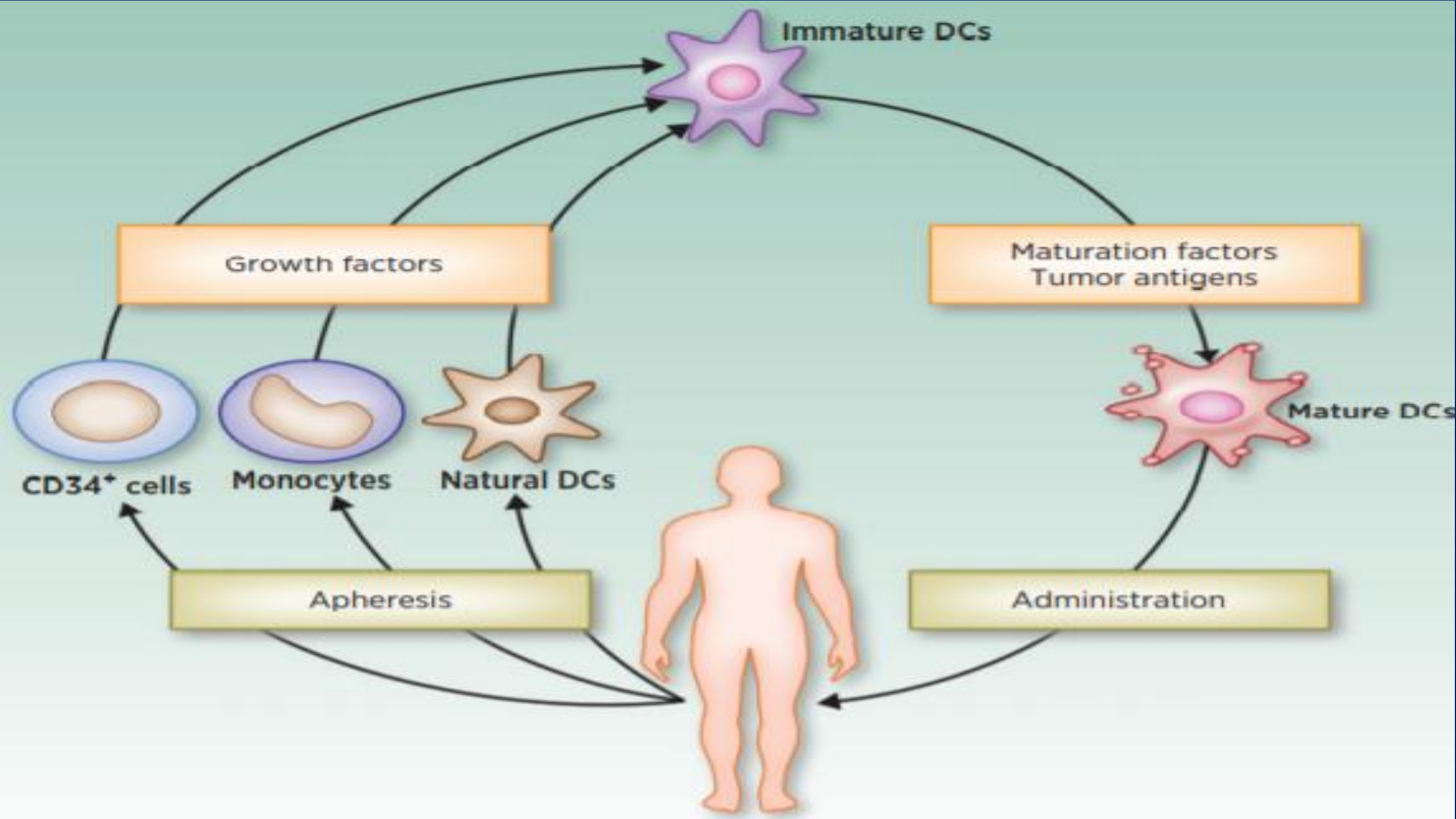

Immature DCs
Growth factors
Maturation factors
Tumor antigens
Mature DCs
CD34+ cells
Monocytes
Natural DCs
Apheresis
Administration

Long-Term Persistence of IgG Antibodies in SARS-CoV Infected Healthcare Workers

(Xiaoqin Guo et al., www.MedRxiv.org, February 14, 2020)

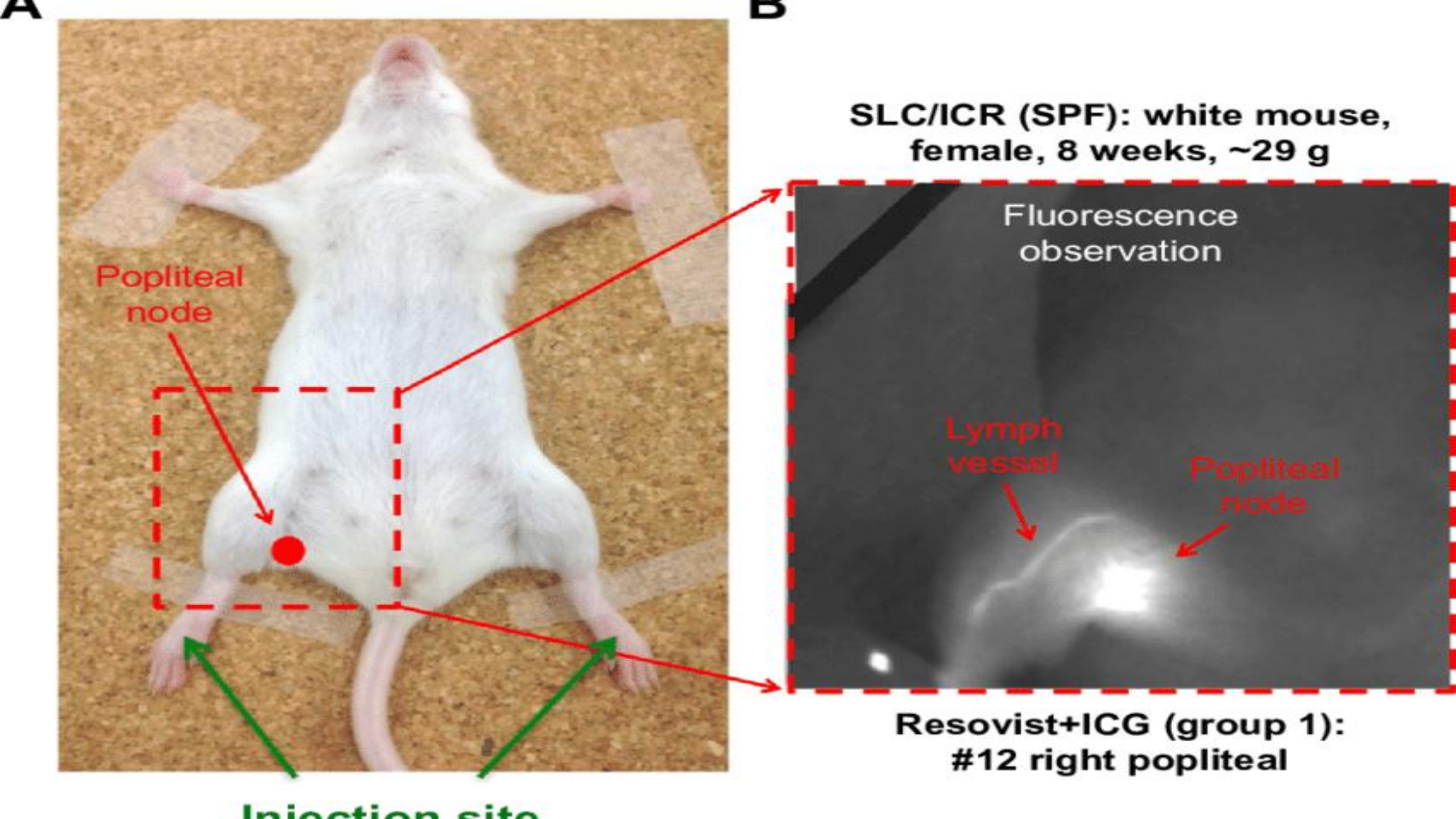
ABSTRACT

BACKGROUND: The ongoing worldwide outbreak of the 2019-nCoV is markedly similar to the severe acute respiratory syndrome (SARS) outbreak 17 years ago. During the 2002-2003 SARS outbreak, healthcare workers formed a special population of patients.

METHODS: A long-term prospective cohort study followed 34 SARS-CoV-infected healthcare workers from a hospital with clustered infected cases during the 2002-2003 SARS outbreak in Guangzhou, China, with a 13-year follow-up. Serum samples were collected annually from 2003-2015. Twenty SARS-CoV-infected and 40 non-infected healthcare workers were enrolled in 2015, and their serum samples were collected. All sera were tested for IgG antibodies with ELISA using whole virus and a recombinant nucleocapsid protein of SARS-CoV, as a diagnostic antigen.

RESULTS: Anti SARS-CoV IgG was found to persist for up to 12 years. IgG titers typically peaked in 2004, declining rapidly from 2004-2006, and then continued to decline at a slower rate. IgG titers in SARS-CoV-infected healthcare workers remained at a significantly high level until 2015. Patients treated with corticosteroids at the time of infection were found to have lower IgG titers than those without.

CONCLUSIONS: IgG antibodies against SARS-CoV can persist for at least 12 years. The presence of SARS-CoV IgG might provide protection against SARS-CoV and other betacoronavirus. This study provides valuable information regarding humoral immune responses against SARS-CoV and the 2019-nCoV.


A
B
Popliteal node
Injection site
SLC/ICR (SPF): white mouse, female, 8 weeks, ~29 g
Fluorescence observation
Lymph vessel
Popliteal node
Resovist+ICG (group 1): #12 right popliteal

- Since the creation of the global stockpile in 2013, more than 50 million doses of Oral cholera vaccines (OCV) have been successfully used in various settings through mass campaigns. OCV is a tool that is used in addition to classic cholera control measures. It should be systematically considered in both endemic cholera hotspots as well as during outbreaks and emergencies.
- OCV are safe and effective and are just one tool in a much larger toolbox that includes sustainable safe water, sanitation, and hygiene (WASH), but serve as a critical bridge to these longer-term efforts.

BIOREACTOR

TURTLE HEALING BAND CLINIC

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NAME: Daniel Royal*

IMMUNITY: SARS-CoV-2

ISSUED: 08-04-20

ANTIBODY: IgG Positive

*Exempt from vaccination pursuant to laboratory testing that verifies this individual has had exposure to the above organism, is "recovered," and is a human subject who is participating in a clinical research study of SARS-CoV-2 with the Crow Tribe of Indians.