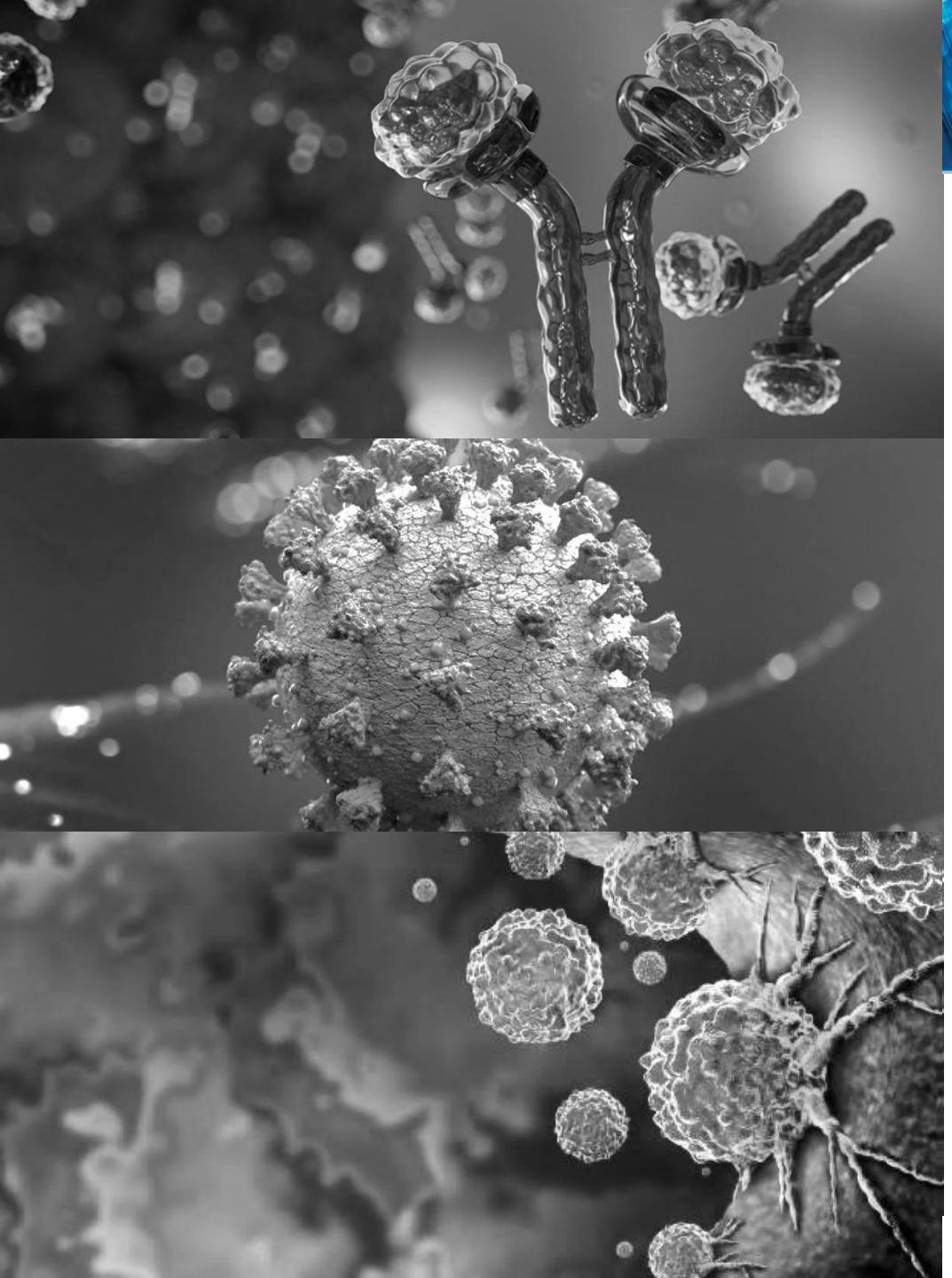


American Urological Association

AUA | Innovation NEXUS

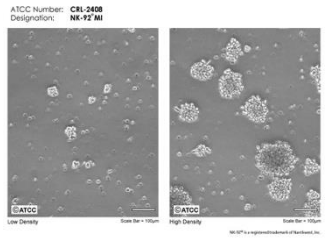
Embracing the Future: The Power of Innovation in a Changing World

Keynote Speaker:
Patrick Soon-Shiong, MBBCh, MSc, FRCS(C), FACS

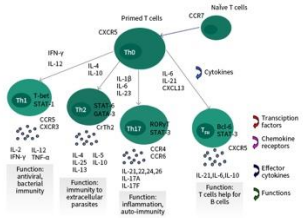
Friday April 25, 2025
1:00 – 1:45pm Pacific

Fighting Dogma: Addressing the Barriers to the Cure

The Power of the Immune System



1992
NK-92 Natural Killer Cell Line Discovered

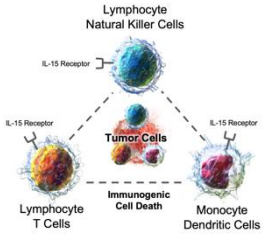


1994
IL-15 Discovered

2005
Abraxane Approved in Breast Cancer
M1 Macrophages

2013
Abraxane Approved in Pancreatic Cancer

The Immune BioShield

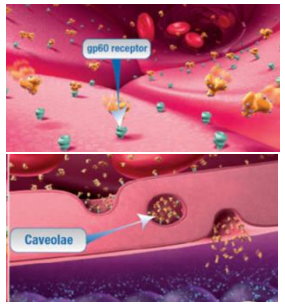


Unlocking the Missing Link

2025
Unveiling a New Class of Immunotherapy:
Lymphocyte Stimulating Agent

1990
Soon-Shiong Publication on NK Cells in Cancer & Transplant Rejection

1993
Nanoparticle Abraxane Concept of Transcytosis Crossing the Blood Vessel Wall



2012
Abraxane Approved in NSCLC
M1 Macrophages

2014
ANKTIVA (IL-15)
Development Begins
Concept of "Avatar Dendritic"

2024
IL-15 Approved for NMIBC

> Horm Metab Res Suppl. 1990:25:215-9.

Prevention of CTL and NK cell-mediated cytotoxicity by microencapsulation

P Soon-Shiong [1], Z N Lu, I Grewal, R Lanza, W Clark

EDITORIAL Open Access

IL-15: from discovery to FDA approval

Zihai Li[1,2,3], John Wrangle[4,5], Kai He[1,2], Jonathan Sprent[6,7] and Mark P. Rubinstein[1,2*]

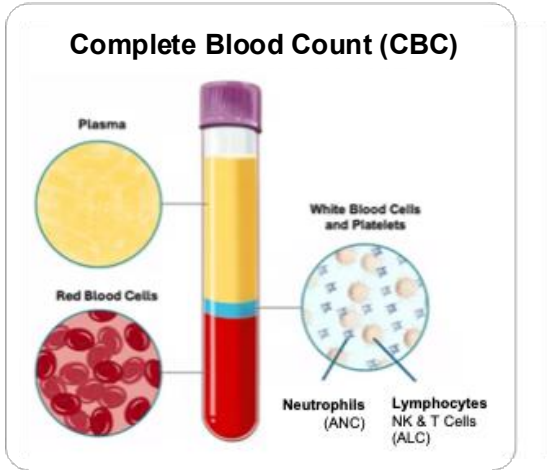
The Missing Link: Lymphopenia

2025 to 2030: Fighting Dogma

The Power of the Immune System in Urology and All Cancers

High Immunosuppressive Neutrophil Count + **Low Lymphocyte Count** = **Recurrence & Low Overall Survival**

(High) **Absolute Neutrophil Count** **ANC** + (Low) **Absolute Lymphocyte Count** **ALC** = $\frac{\textbf{High ANC}}{\textbf{Low ALC}}$ = **High Neutrophil Lymphocyte Ratio**



The Barrier to the Cure

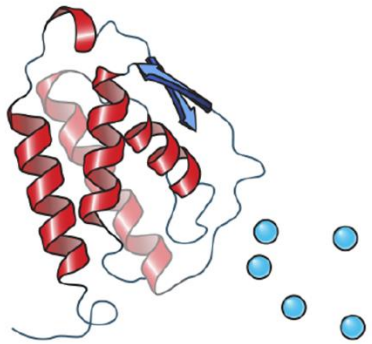
2025 to 2030: Fighting Dogma

The Power of the Immune System in Urology and All Cancers

Overcoming the Barriers to the Cure

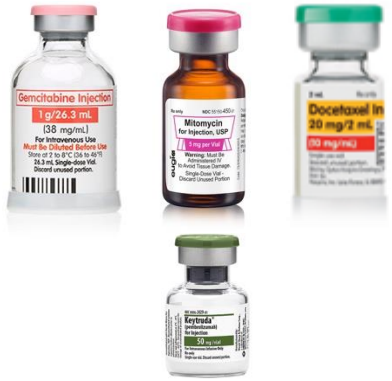
High Immunosuppressive Neutrophil Count + **Low Lymphocyte Count** = **Recurrence & Low Overall Survival**

(High) **Absolute Neutrophil Count** **ANC** + (Low) **Absolute Lymphocyte Count** **ALC** = **High ANC / Low ALC** = **High Neutrophil Lymphocyte Ratio**



GM-CSF

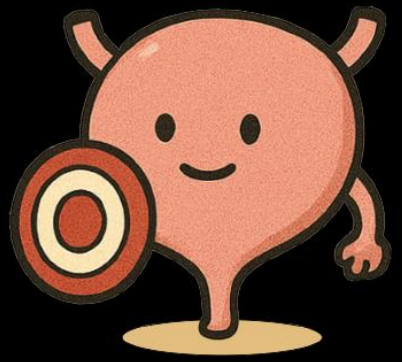
+



Chemotherapies & CPIs

= ***Win the Battle… Lose the War***

The Bladder's Quantum State



Immune Protected Healthy Bladder

NK, T Cells, and Memory T Cells

Immune Compromised Bladder

GM-CSF Suppressor Neutrophils Myeloid Derived Suppressor Cells

Crippled Painful Bladder

Chemotherapy Lymphopenia

The Lost Bladder

Total Radical Cystectomy

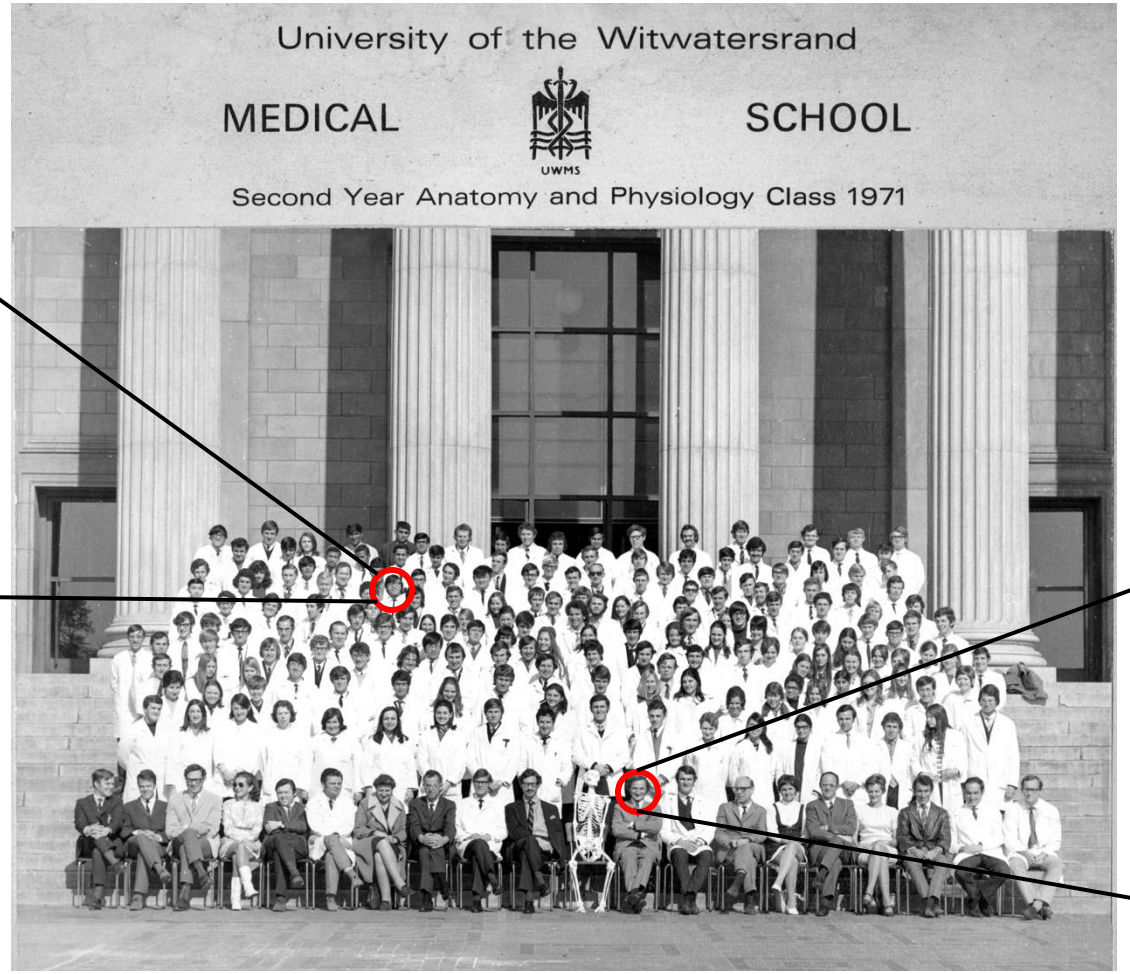
Never quit…
Fight dogma…
Ignore naysayers…
Follow the science…
Follow your passion…
Courage of your convictions…
Purposeful impactful innovation…

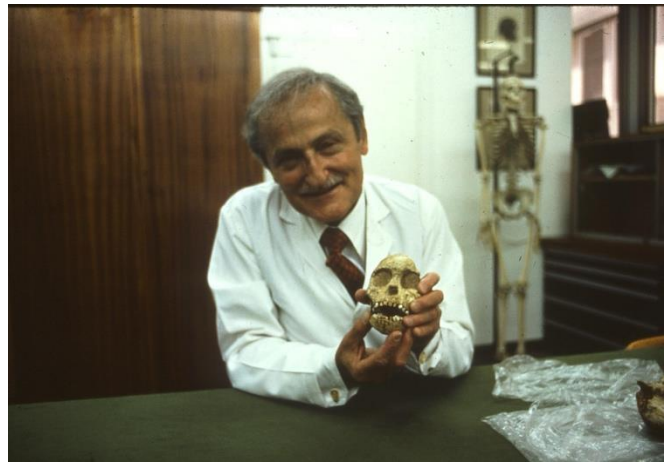
The only interest to be considered is that of your patients

Patrick Soon-Shiong, MBBCh, MSc, FRCS(C), FACS

Journey from Apartheid to Academia

1971: University of Witwatersrand South Africa



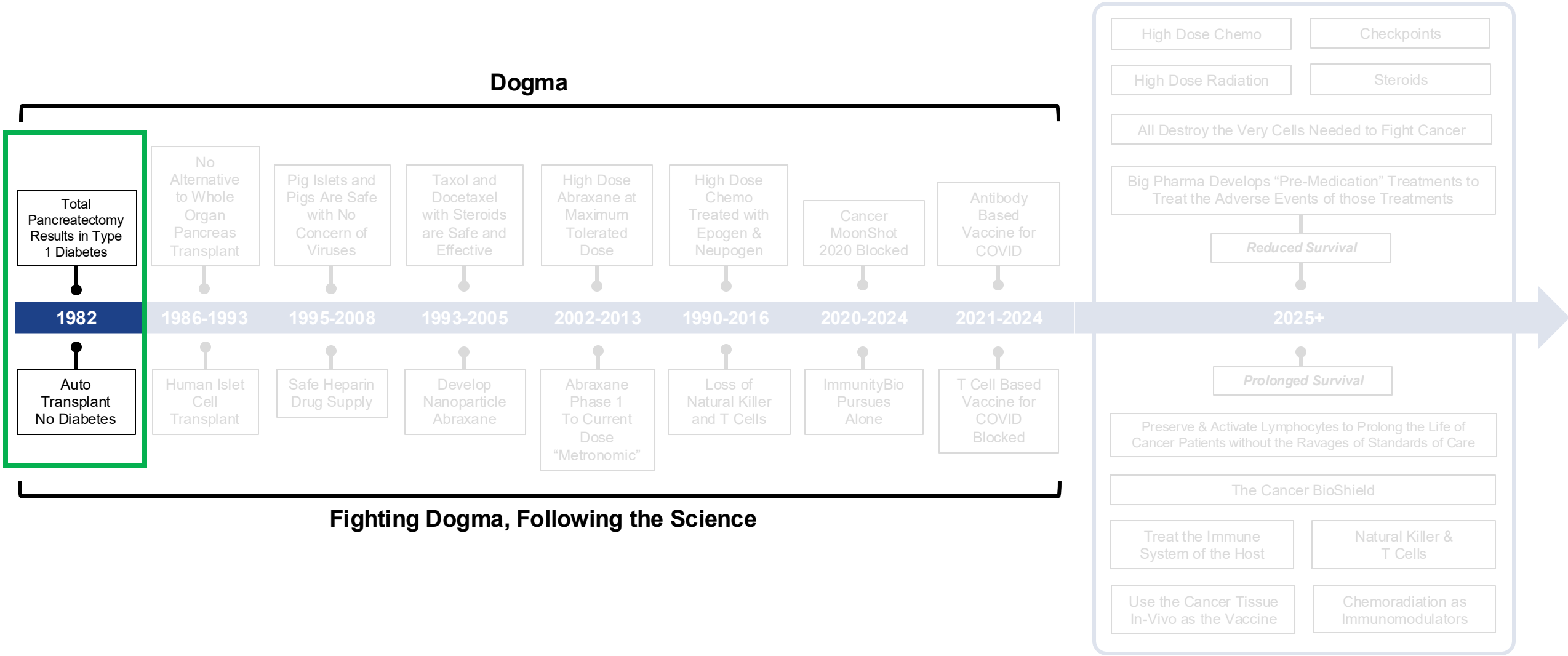


Professor Phillip V Tobias

June 1976: Apartheid in South Africa

Fight Dogma, Follow the Science and Ignore Naysayers

"The only interest to be considered is the interest of the patient"



1982: Auto Transplant of Whole Pancreas

Pancreas
Vol. 2, No. 3, pp. 357–361

Case Report

Successful Long-Term Exocrine and Endocrine Function of the Autotransplanted Pancreas in Humans

*Patrick Soon-Shiong, †Gerald Swafford, and *Seymour Levin

*Departments of Surgery and Medicine, UCLA Medical Center, Los Angeles, and †Department of Surgery, University of California, Davis, Davis, California, U.S.A

Case Reports > Pancreas. 1988;3(6):740-1. doi: 10.1097/00006676-198812000-00016.

Absence of the "incretin" phenomenon in the autotransplanted human pancreas

P Ginier, S R Levin, G Swafford, P Soon-Shiong

PMID: 3065778 DOI: 10.1097/00006676-198812000-00016

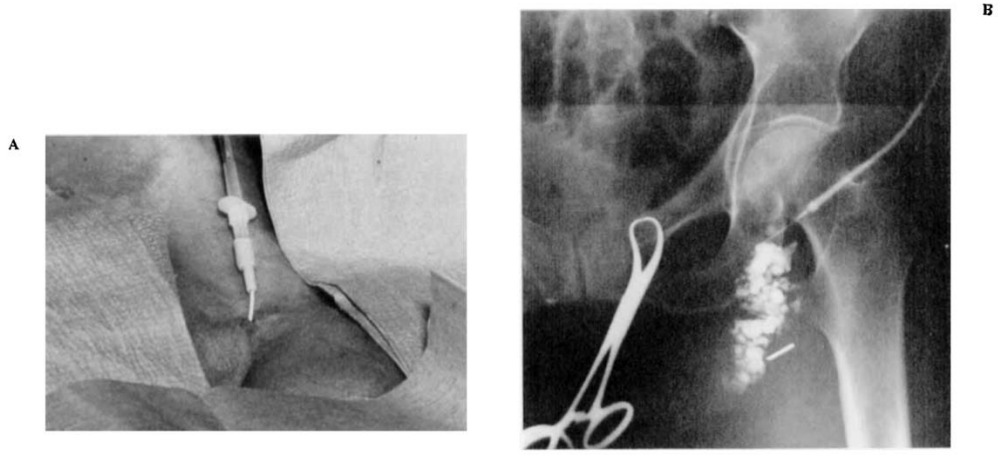


FIG. 1. A: Cannulation of pancreatic duct in left groin. B: Pancreaticogram of the transplanted duct, indicating its dilated and tortuous nature.

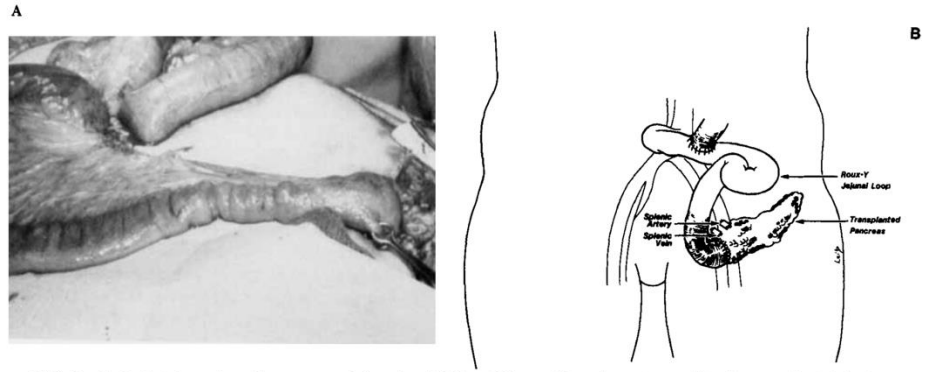
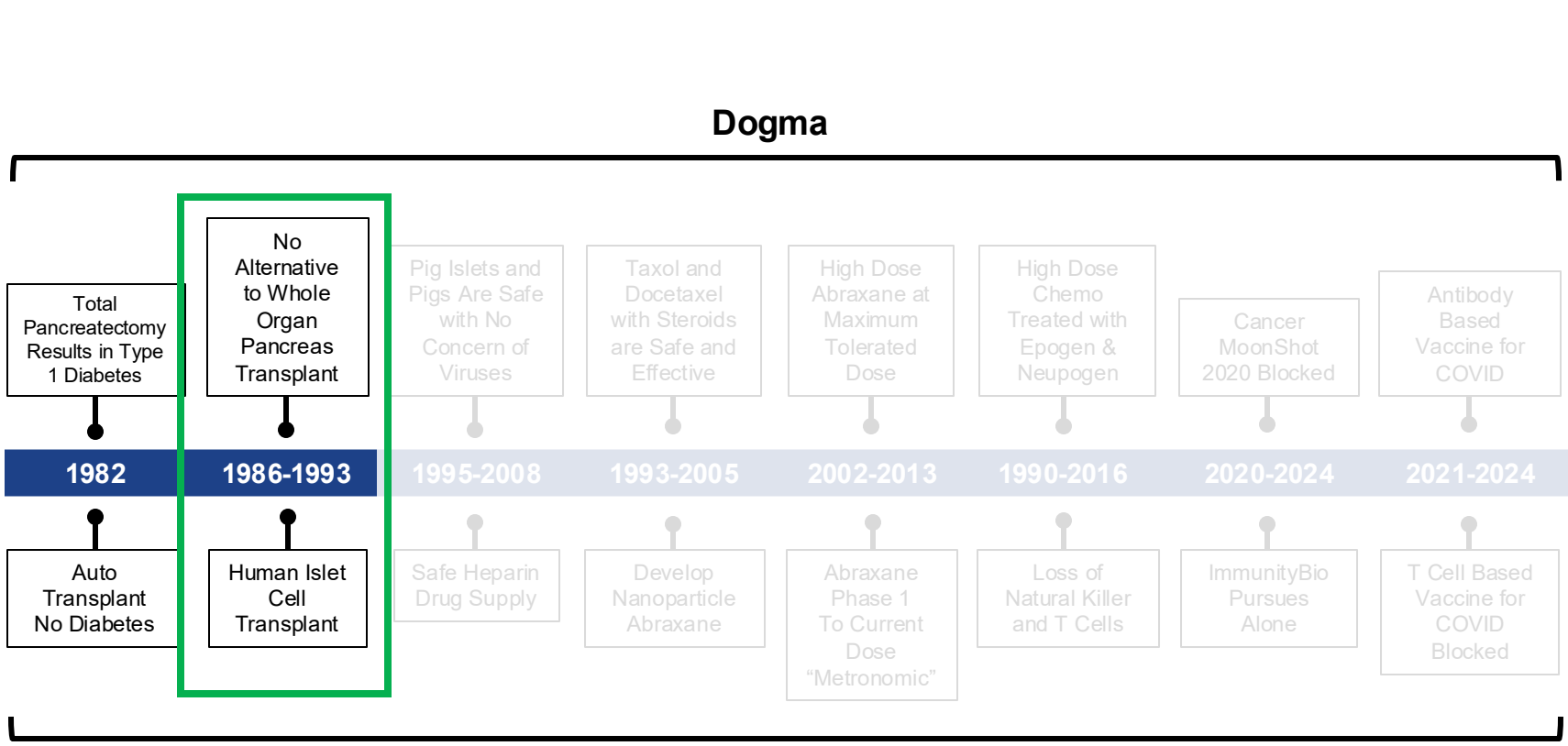


FIG. 2. A, B: Autotransplanted pancreas to left groin with Roux-Y loop of bowel anastomosed to the transplanted duct.

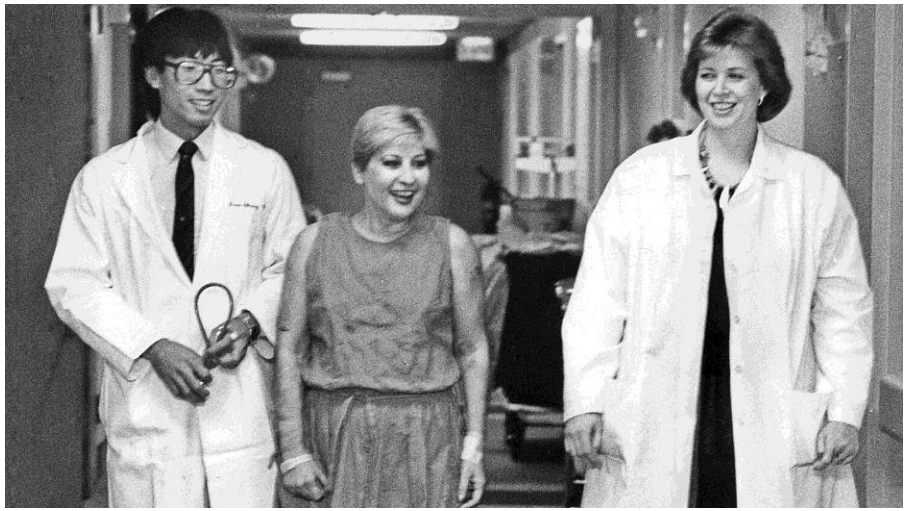
Dr. Patrick Soon-Shiong
Surgical Chief Resident
UC Davis 1985

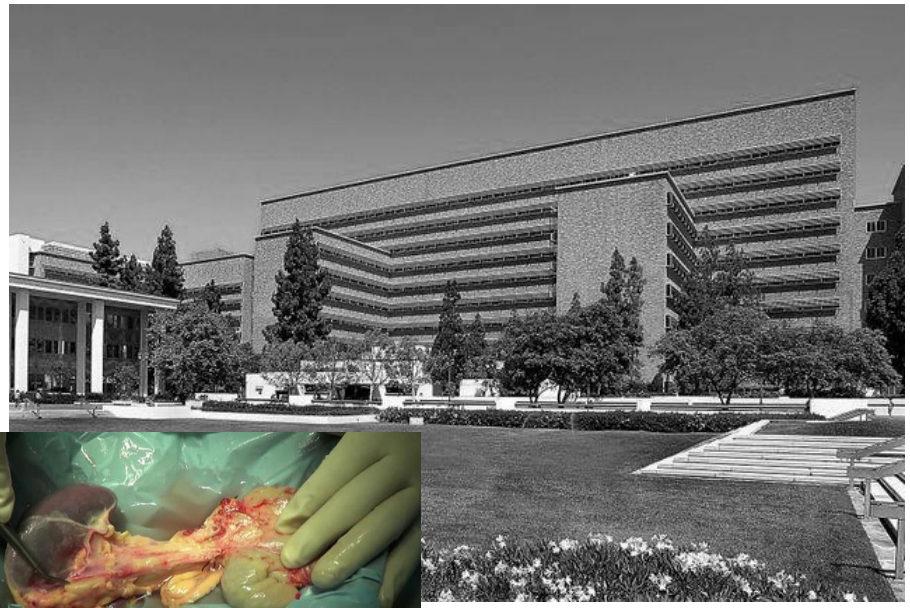
Fight Dogma, Follow the Science and Ignore Naysayers

"The only interest to be considered is the interest of the patient"



Dec 5, 1986: West Coast's 1st Pancreas Transplant





West Coast's 1st Pancreas Transplant

By SUE HORTON

It certainly wasn't a gourmet feast, but to Clara Clements it seemed like one. There was soup and chicken, rice and bread. And, Clements recounted with delight, "There was coffee cake. I had a piece of cake."

For 20 years since coming down with diabetes, Clements, a 40-year-old Glendale resident, had been on a restricted diet in which sugars and starchy foods were taboo.

Then last month, she had a pancreas transplant at UCLA Medical Center, the first such operation performed on the West Coast. On Thursday, Clements was well enough to leave the hospital after a 3½-week stay.

First Unrestricted Dinner

After the operation, Clements had something most diabetics don't even dare hope for—a healthy pancreas capable of producing sufficient insulin to control her blood-sugar levels. Several days after the operation she ate her first unrestricted dinner.

"When she saw that first meal, her eyes gleamed," said Dr. Patrick Soon-Shiong, the UCLA surgeon who performed Clements' transplant. "She told me she had been waiting for that day for 20 years. That is what this operation is all about—improving the quality of life for patients with severe diabetes."

Pancreas transplant surgery is still in its infancy. To date, only about 900 pancreas transplants have been performed worldwide. Currently, four pan-

See TRANSPLANT, Page 34

Los Angeles Times

Los Angeles Times

PANCREAS: First West Coast Transplant

Continued from Page 34

have a successfully functioning new pancreas.

Long-term success rates are unknown because the procedure is so new. Although the first pancreas transplant was performed at the University of Minnesota in 1966, it has only been recently that such transplants have been widely available. The majority of pancreas transplants have been performed in Minnesota. The procedure is also done at the University of Iowa and the University of Wisconsin at Madison.

Not Recommended for All

Soon-Shiong is quick to point out that the surgery is not recommended for all diabetics. At UCLA, pancreas transplants will only be performed on people with the most severe form of the disease who've already had a kidney transplant operation. Cancer patients are not candidates for the operation at this times.

Significant numbers of diabetic have needed kidney transplants, Soon-Shiong said, estimating that 25% to 30% of all kidney transplants are necessitated by kidney failure due to severe diabetes.

Patients who previously had kidney transplants are already taking drugs to suppress their immune systems to minimize the chance of rejection. These immunosuppressants can have serious side effects, including increasing the risk of infection in patients taking them. Therefore patients who are already taking the drugs are considered better candidates for pancreas transplants. Otherwise, we would be "simply substituting anti-rejection drugs for insulin," Soon-Shiong said.

JOSE GALVEZ / Los Angeles Times

Patient Clara Clements, right, and Dr. Patrick Soon-Shiong.

With the addition of a pancreas transplant program, UCLA has become one of the few centers in the country to provide all four types of major organ transplants. Heart, liver and kidney transplants are the other types of organ transplants.

UCLA began performing the procedure, Soon-Shiong said, as part of a continuing program to provide the best possible medical care to diabetes sufferers.

In addition to its transplant program, UCLA is studying alternative ways of stimulating insulin production in patients with severe diabetes. Researchers are currently focusing on transplanting islet cells from the pancreas, the cells specifically responsible for producing insulin. The procedure has been tried unsuccessfully nationwide on about 115 patients.

UCLA doctors plan to continue performing pancreas transplants as organs become available and as patients need them.

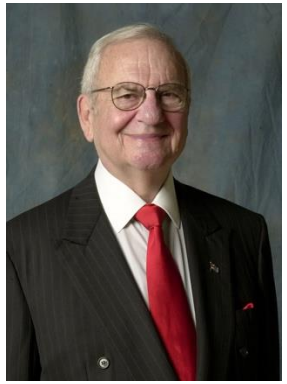
Clara Clements thinks that is just great. "I would say to other patients, 'Go ahead.' The first day I heard about the program I was very nervous. Then I thought 'I'm going to be able to eat what I've missed eating for 20 years and I won't have to give myself insulin.' That decided me."

Horton lives in Los Angeles.

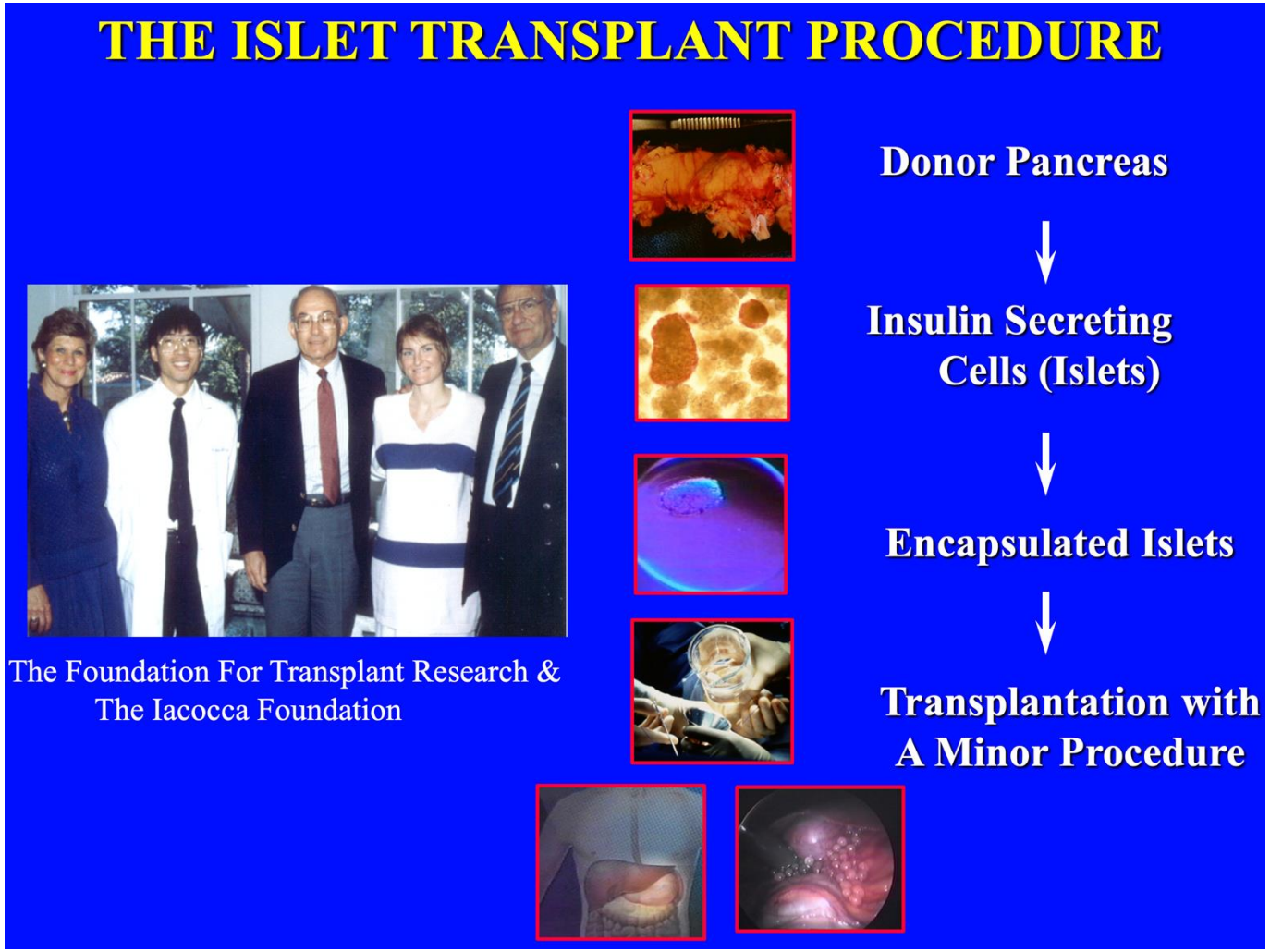
Whale Watching Trips

The American Cetacean Society will sponsor three, early spring whale watching trips to Baja California, Mexico. The trips will be on Feb. 25 to March 5 (to San Ignacio Lagoon), March 29 to April 5 (to the Sea of Cortez) and May 20 to 21 (also to the Sea of Cortez). Information: (213) 541-9010.

1988: Moving From Whole Organ Transplant to Encapsulated Islet Cell Innovation

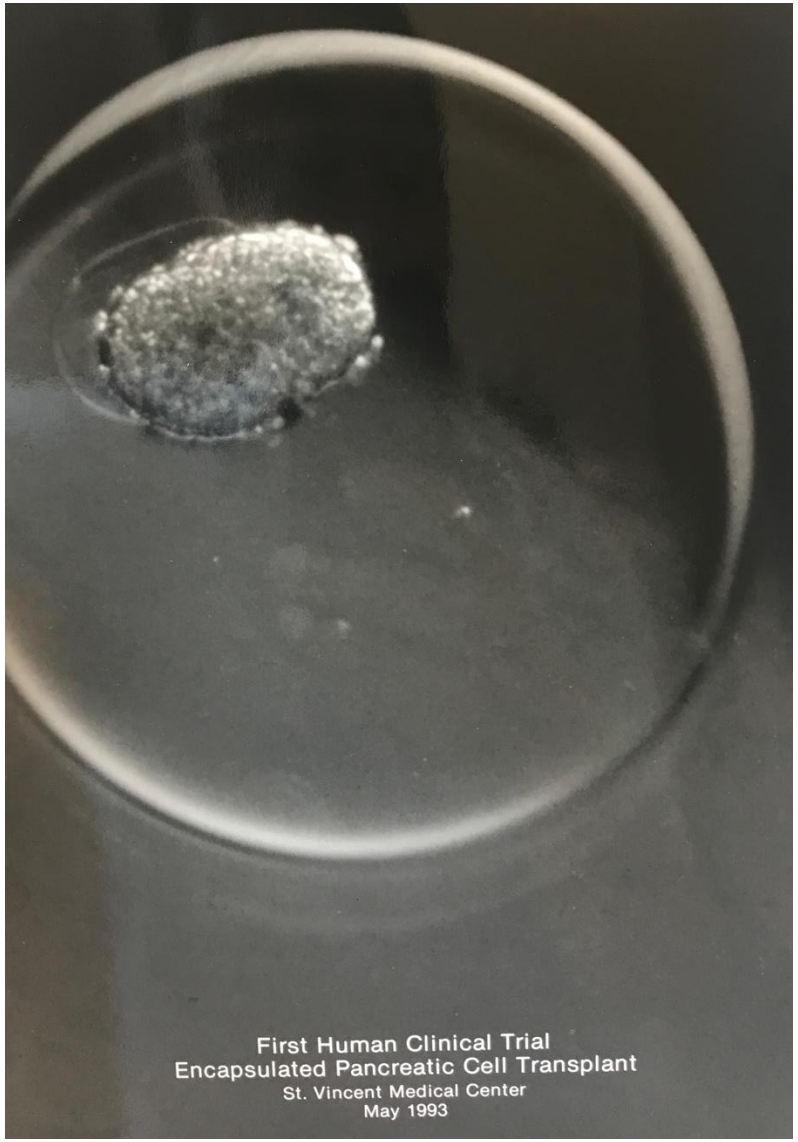


Lee Iacocca



1993: World's First Encapsulated Islet Cell Transplant

Feeling Fine, Looking Good - Steven Craig, 38, Lake Isabella, CA., left, enjoyed his first breakfast without insulin in 30 years, two days after undergoing the first human encapsulated intraperitoneal pancreatic islet cell transplant. The minimally invasive surgery was performed May 6, 1993 by Dr. Patrick Soon-Shiong, director, Islet Transplant Center, St. Vincent Medical Center, Los Angeles.



ST. VINCENT MEDICAL CENTER

Volume No. 2 Number 2 Summer 1993

MEDICAL SCIENCE NEWS

Revolutionary New Diabetes Treatment Used In Historic First Human Trial At Medical Center.

St. Vincent Medical Center was the site May 6 of the first human encapsulated pancreatic islet cell transplant.

"This FDA-approved clinical trial in humans is the first step in evaluating the potential of encapsulated islets as a new therapy for treating the estimated 1.4 million insulin-dependent diabetics in the U.S., without the need for life-long immuno-suppression," said Patrick Soon-Shiong, M.D., of SVMC's National Institute of Transplantation. "Although the transplant of encapsulated pancreatic cells has successfully reversed diabetes in animal research studies, we have much to learn about the application of this technique in human diabetes."

Dr. Soon-Shiong's successful animal studies were reported in the June

SVMC was the site in May of the first human transplant of encapsulated pancreatic islet cells, a potential new therapy for insulin-dependent diabetics.

Clarrisa Hooper, 35, Long Beach, CA., left, was off insulin for the first time in 22 years just two days after undergoing the second human encapsulated pancreatic islet cell transplant on Monday, January 24, 1994. This minimally invasive procedure was first performed in May, 1993 by Patrick Soon-Shiong, M.D., right director of the Islet Transplant Center, St. Vincent Medical Center, Los Angeles.

January 28, 1994 – Islet Cell Transplant

THE LANCET

Short reports

Insulin independence in a type 1 diabetic patient after encapsulated islet transplantation

Patrick Soon-Shiong, Roswitha E Heintz, Noma Merideth, Qiang X Yao, Zhiwen Yao, Tianli Zheng, Michael Murphy, Molly K Moloney, Marcia Schmehl, Michael Harris, Robert Mendez, Raphael Mendez, Paul A Sandford

Identification of a biocompatible immunoprotective membrane to prevent graft rejection remained elusive until the development of microcapsules formulated in alginate high in guluronic acid. We report insulin independence in a type 1 diabetic patient after encapsulated islet transplantation. Encapsulated human islets were injected intraperitoneally in a diabetic patient with a functioning kidney graft. Insulin independence with tight glycaemic control was demonstrated 9 months after the procedure. These results warrant a trial of a high dose of encapsulated islets in early-onset diabetic patients.

Lancet 1994; **343:** 950–51

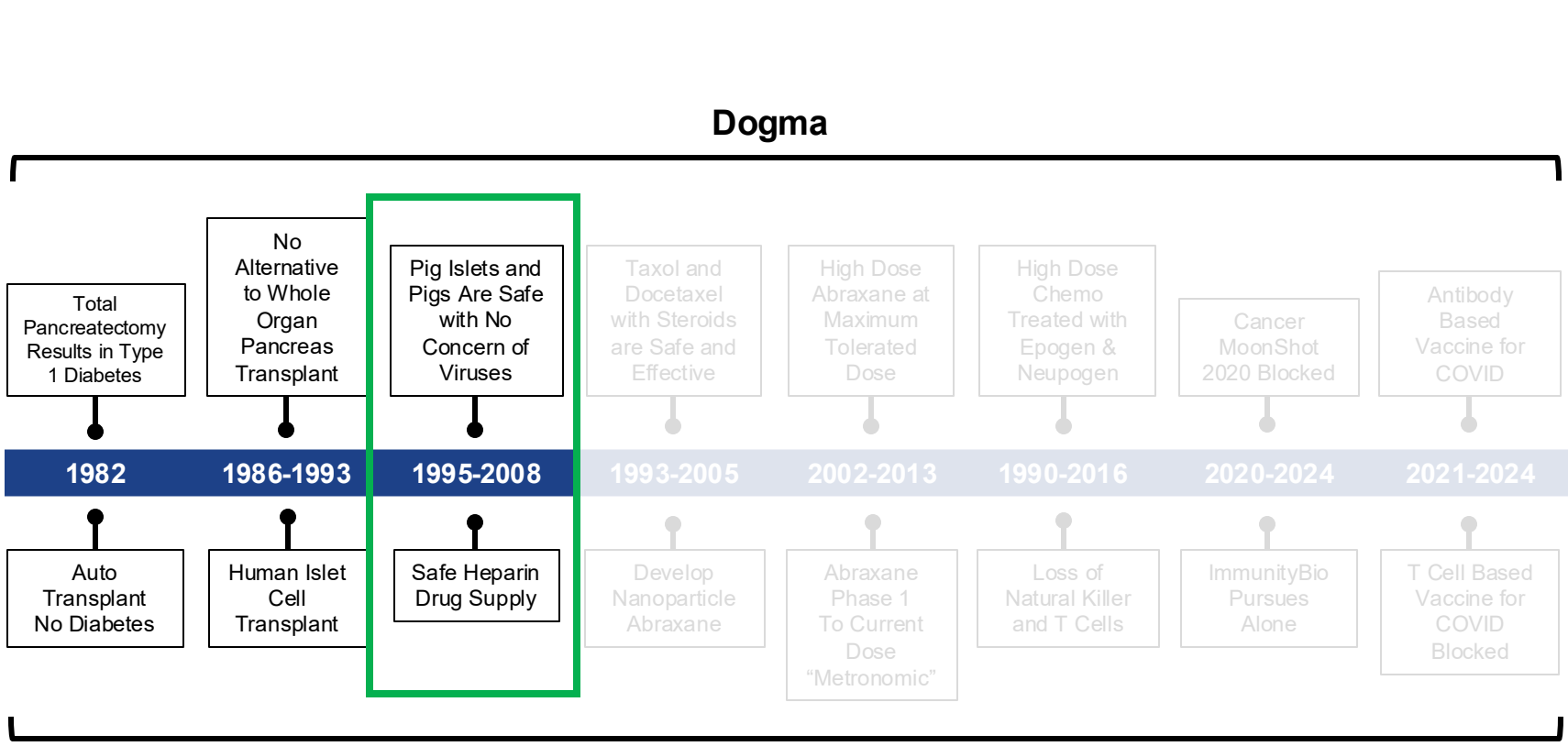
The patient is a 38-year-old man who has had insulin-dependent diabetes for 30 years, requiring a mean of 0·7 (SE 0·01) U insulin per kg per day (45–50 U daily). The patient had severe complications, including lower extremity peripheral neuropathy (daily, sharp shooting pains of the left lower foot with progressive sensory loss), foot ulcers, retinopathy, and end-stage renal failure resulting in a living-related kidney transplantation. His renal function was stable (serum creatinine 8·8 μmol/L) on low-dose maintenance immunosuppression of cyclosporin and azathiopine 50 mg daily. Our patient did not receive the induction immunotherapy routinely prescribed in trials of unencapsulated islets, and his low-dose maintenance cyclosporin was unchanged during follow-up. Thus, while further trials on non-immunosuppressed patients are needed to demonstrate the immunoprotectivity of the capsules without immunosuppression, as has been shown in the large animal studies,[10] we have demonstrated immunoprotectivity of the capsule under these low-dose conditions.

Human islets were isolated from eight cadaveric donor pancreases by standard collagenase digestion and purified by gradient separation. An islet purity of 85% was obtained with a yield of 1166 999 (actual count) or 960 331 (150 μm equivalent count). After a mean culture period of 22 (SE 16) days, 678 000 encapsulated islet equivalents with a mean insulin stimulation index of 30 (11) were pooled for transplantation. Via a 2 cm midline abdominal incision, the encapsulated islets at 9957/kg were transplanted into the peritoneal space. On the basis of our pre-clinical data, we estimate that a full therapeutic dose of encapsulated islets would be 20 000 per kg. 6 months after the initial dose of about 10 000 islets per kg, the patient received a supplemental dose of 5000 islets per kg as part of a dose-escalation study.

https://pubmed.ncbi.nlm.nih.gov/7909011/

Fight Dogma, Follow the Science and Ignore Naysayers

"The only interest to be considered is the interest of the patient"



1997: Courage of Your Conviction

Refusing to Perform Unsafe Pig Islet Transplant

"The only interest to be considered is the interest of the patient"

ARTICLES

Infection of human cells by an endogenous retrovirus of pigs

CLIVE PATIENCE, YASUHIRO TAKEUCHI & ROBIN A. WEISS

Chester Beatty Laboratories, The Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, UK

The possible use of pig organs and tissues as xenografts in humans is actively being considered in biomedical research. We therefore examined whether pig endogenous retrovirus (PERV) genomes can be infectiously transmitted to human cells in culture. Two pig kidney cell lines spontaneously produce C-type retrovirus particles. Cell-free retrovirus produced by the PK-15 kidney cell line (PERV-PK) infected pig, mink and human kidney 293 cell lines and co-cultivation of X-irradiated PK-15 cells with human cells resulted in a broader range of human cell infection, including human diploid fibroblasts and B- and T-cell lines. Kidney, heart and spleen tissue obtained from domestic pigs contained multiple copies of integrated PERV genomes and expressed viral RNA. Upon passage in human cells PERV-PK could rescue a Moloney retroviral vector and acquired resistance to lysis by human complement.

The number of patients requiring organ or tissue transplantation far outweighs the availability of suitable human donor organs and xenotransplantation of non-human primate and pig organs is therefore being viewed as a means to alleviate this shortage of donor organs[1–3]. Although baboon to human xenotransplants have been attempted[4,5], most attention is being focused upon the pig as a suitable donor of cells, tissues and vascularized organs due to a variety of practical, financial, safety and ethical reasons[1,2].

xenografted recipient. Retroviruses fall into this category[14,15].

The normal germ line DNA of many vertebrate species, including humans, contains sequences related to infectious exogenous retroviruses[16–18]. Such endogenous retroviruses (ERV) might cause disease if transmitted as a zoonosis, even when they are not normally pathogenic in their natural host species. It is already known that an endogenous virus of baboons (BaEV), one of cats (RD114) and some of mice can infect and replicate in human cells[18–20]. Indeed, RD114 was first detected as a virus contaminat-

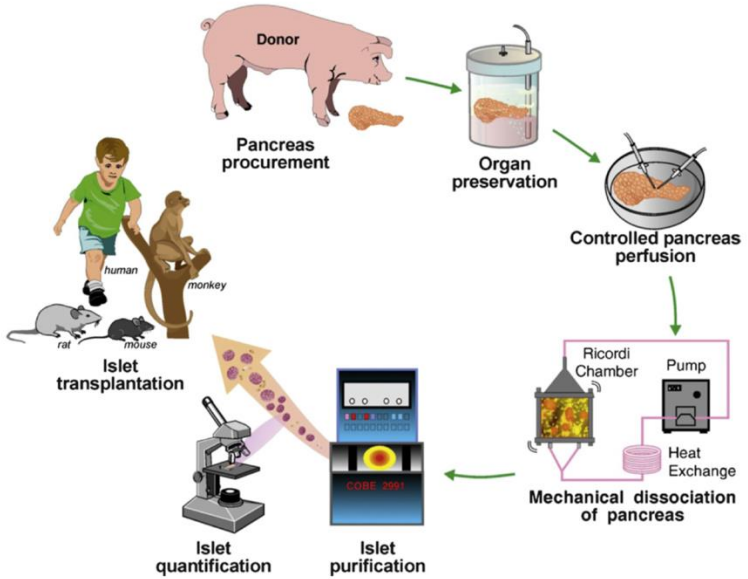


Figure 4 Schematic diagram of the method used for the isolation of islets from adult pigs.

Mylan Laboratories Inc. v. Soon-Shiong (1999)

- Voluntarily requests FDA to place trial on hold
- Refuses to perform pig islet cell transplant despite urging to do so by the board

2008: Lesson Learned About Safe Pigs

Providing Nation's Safe Heparin Supply

Nightline – Heparin Contamination

2008

Report Confirms Source of Contaminated Heparin

By ABC News
December 3, 2008, 8:02 PM

Dec. 4 -- WEDNESDAY, Dec. 3 (HealthDay News) -- A final report on the deadly contamination of the blood thinner heparin confirms that the problem was caused by a man-made chemical that was added to batches of the drug imported from China, U.S. investigators report.

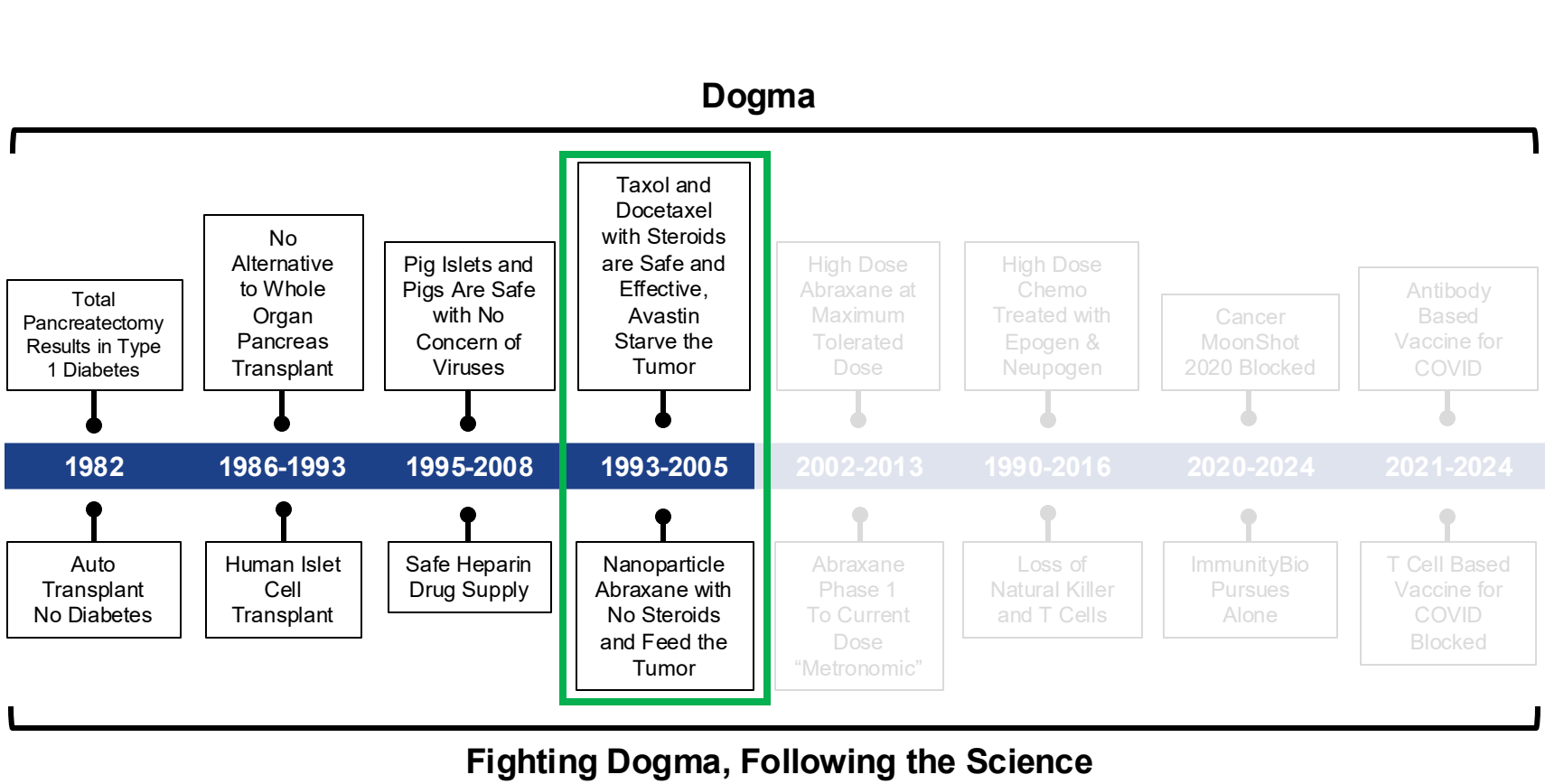
The crisis, which began last November, resulted in 152 adverse reactions and as many as 81 deaths in the United States. The Chinese heparin, contaminated with the chemical oversulfated chondroitin sulfate, was found in at least 10 countries, according to federal officials.

2008
Safe Supply of Heparin

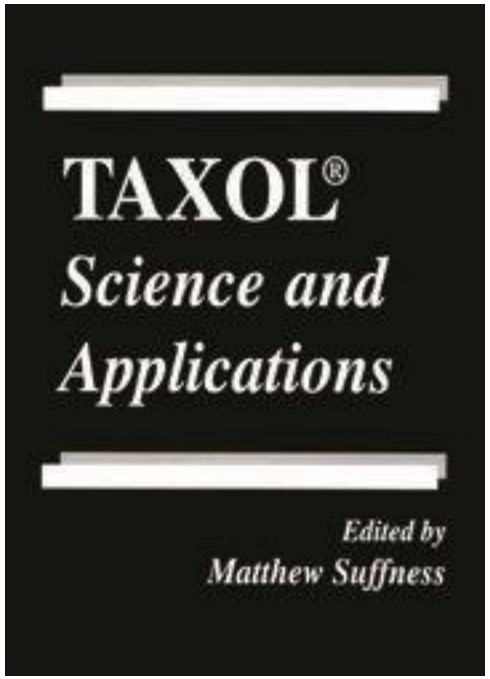
APP AMERICAN PHARMACEUTICAL PARTNERS, INC.

Fight Dogma, Follow the Science and Ignore Naysayers

"The only interest to be considered is the interest of the patient"



1992: Taxol - Anaphylaxis and Death Despite Steroid Treatment



This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

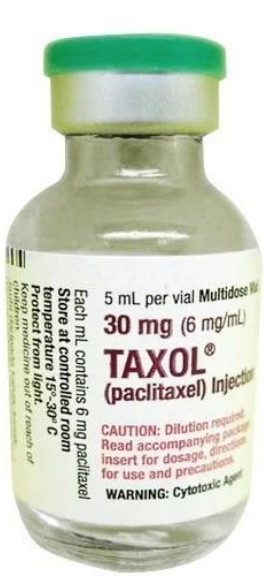
TAXOL® (paclitaxel) INJECTION **Rx only**
(Patient Information Included)

WARNING

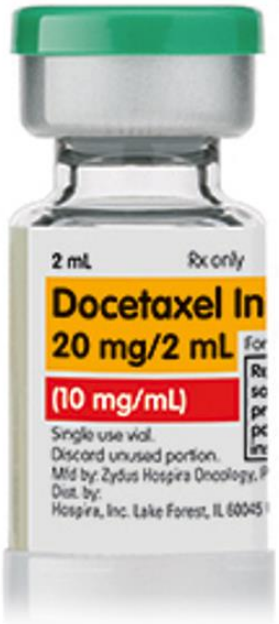
TAXOL® (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See **DOSAGE AND ADMINISTRATION**.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

TAXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.



BMS



Sanofi

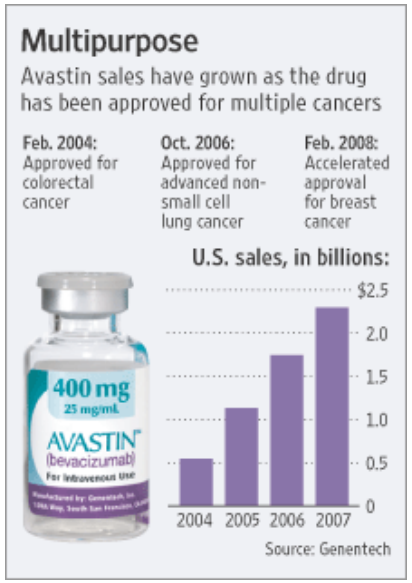
2005: Starve the Tumor - Genentech

Table 1 Timeline of Bevacizumab for Metastatic Breast Cancer

Date	Action
December 2005	The randomized, phase 3 E2100 trial presented at a national meeting, showing a 5.5-month increase in median PFS with the addition of bevacizumab to paclitaxel for metastatic breast cancer.[a] (Results published in the *New England Journal of Medicine* in 2007.[b])
December 2007	ODAC recommends against approval of bevacizumab for metastatic breast cancer to FDA, citing the lack of OS benefit in the E2100 study.
February 2008	FDA grants conditional accelerated approval for bevacizumab with paclitaxel as first-line therapy for metastatic breast cancer contingent upon confirmatory trials to further define benefits.
July 2010	ODAC meets to review the 2 confirmatory trials,[c,d] and recommends to FDA to remove the breast cancer indication from the label, citing an unfavorable risk-to-benefit profile.
September 2010	FDA announces it will delay its decision regarding converting the accelerated approval to a full approval or removing the breast cancer indication.
December 2010	FDA proposes removing the metastatic breast cancer indication from bevacizumab label.
January 2011	The manufacturer (Genentech) files an appeal with FDA and requests an administrative hearing that is open to the public.
June 28, 2011	FDA and ODAC conduct 2-day public hearing involving data presentations from the manufacturer and testimonials from patients and physicians, accompanied by expansive media coverage and patient advocacy group demonstrations.
June 30, 2011	ODAC votes unanimously against allowing the breast cancer indication to remain on the label; however, the FDA allows public comments to be submitted until July 28, 2011.
August 5, 2011	The manufacturer files an appeal of decision in its posthearing summary, with proposed labeling changes.
September 2011	A final decision is awaited from FDA Commissioner.

[a]Miller KD, Wang M, Gralow A, et al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). Presented at: 28th Annual San Antonio Breast Cancer Symposium; December 8-11, 2005; San Antonio, TX.
[b]Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007;357:2666-2676.
[c]Miles DW, Chan A, Dirix LY, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.* 2010;28:3239-3247.
[d]Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol.* 2011;29:1252-1260.

FDA indicates US Food and Drug Administration; ODAC, Oncologic Drugs Advisory Committee; OS, overall survival; PFS, progression-free survival.



Genentech

PHARMA

FDA Commissioner announces Avastin decision

• Nov 18, 2011 11:20am

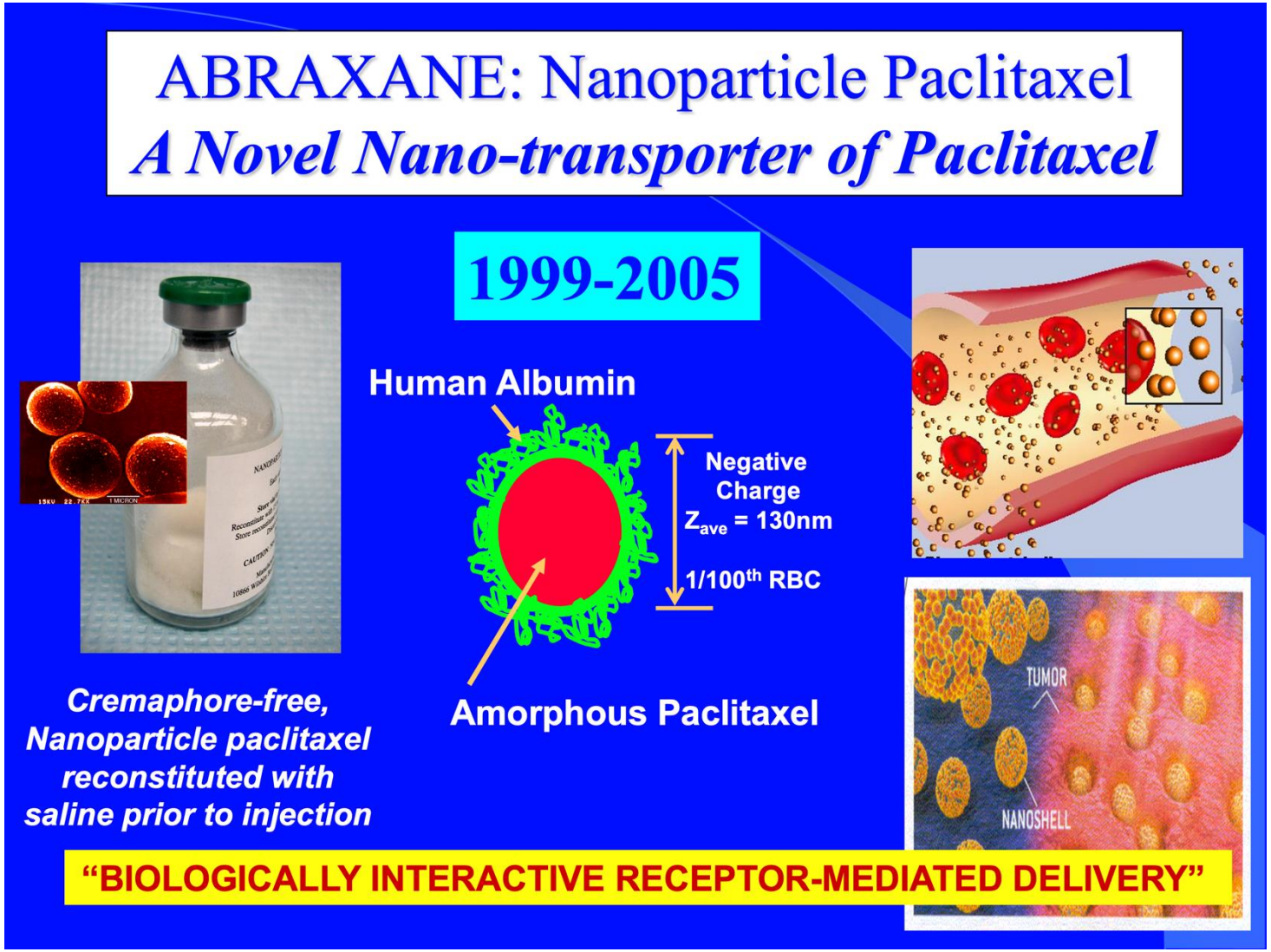
Pharma

Drug not shown to be safe and effective in breast cancer patients

SILVER SPRING, Md., Nov. 18, 2011 /PRNewswire-USNewswire/ --FDA Commissioner Margaret A. Hamburg, M.D., said today she is revoking the agency's approval of the breast cancer indication for Avastin (bevacizumab) after concluding that the drug has not been shown to be safe and effective for that use.

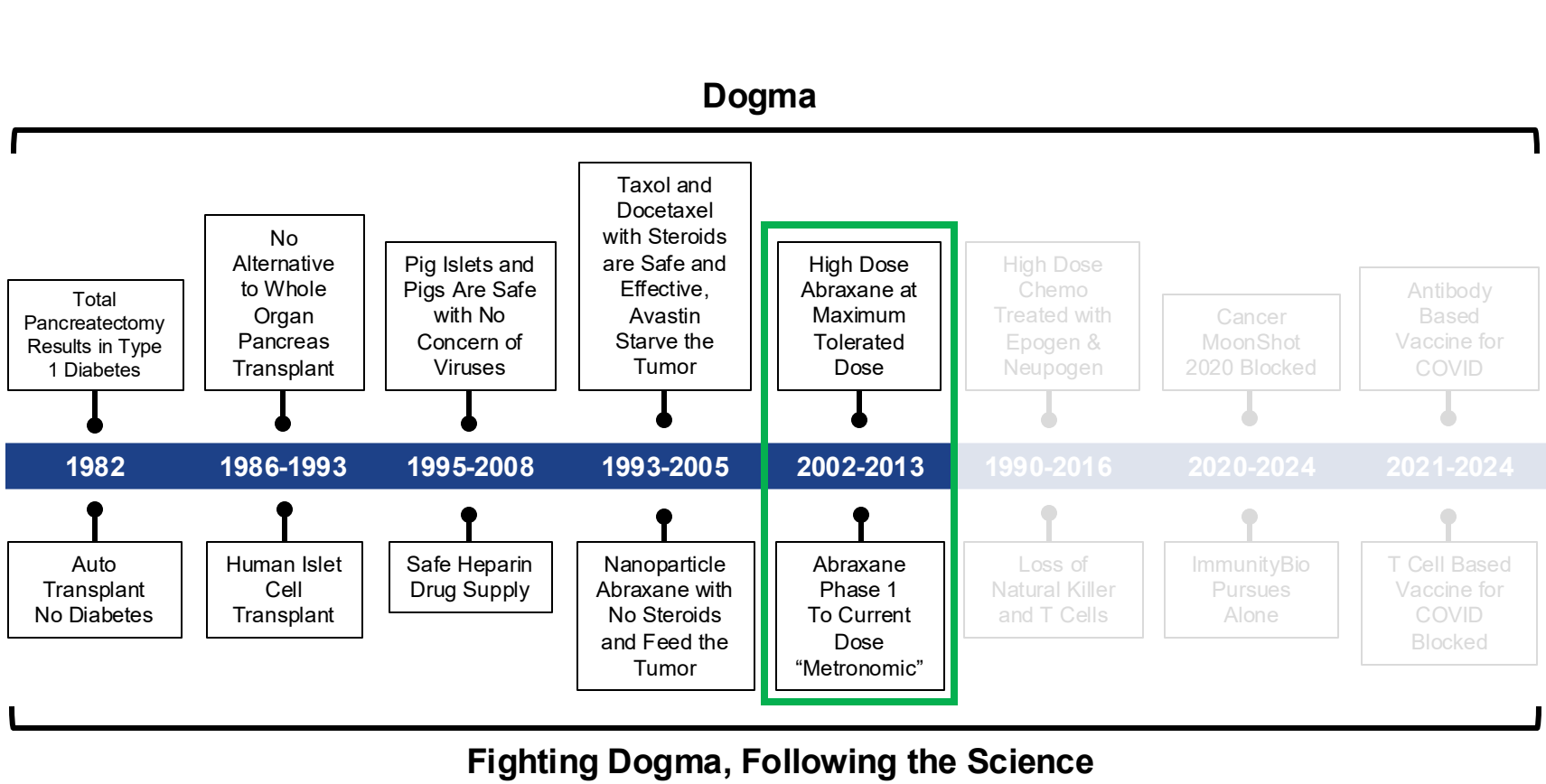
1999-2005: Feed the Tumor
Activate the Immune System: M1 Macrophages

Abraxane



Fight Dogma, Follow the Science and Ignore Naysayers

"The only interest to be considered is the interest of the patient"



Chemotherapy Causes Lymphopenia

"Courage of your conviction, refusal to pursue maximum tolerated dose of 300mg/m2"

Clinical Trial > Clin Cancer Res. 2002 May;8(5):1038-44.

Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel

Nuhad K Ibrahim [1], Neil Desai, Sewa Legha, Patrick Soon-Shiong, Richard L Theriault, Edgardo Rivera, Bita Esmaeli, Sigrid E Ring, Agop Bedikian, Gabriel N Hortobagyi, Julie A Ellerhorst

Affiliations – collapse

Affiliation

1 Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston 77030, USA.

PMID: 12006516

Abstract

Purpose: ABI-007 is a novel Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. The absence of Cremophor EL may permit ABI-007 to be administered without the premedications used routinely for the prevention of hypersensitivity reactions. Furthermore, this novel formulation permits a higher paclitaxel concentration in solution and, thus, a decreased infusion volume and time. This Phase I study examines the toxicity profile, maximum tolerated dose (MTD), and pharmacokinetics of ABI-007.

Experimental design: ABI-007 was administered in the outpatient setting, as a 30-min infusion without premedications. Doses of ABI-007 ranged from 135 (level 0) to 375 mg/m2 (level 3). Sixteen patients participated in pharmacokinetic studies.

Results: Nineteen patients were treated. No acute hypersensitivity reactions were observed during the infusion period. Hematological toxicity was mild and not cumulative. Dose-limiting toxicity, which occurred in 3 of 6 patients treated at level 3 (375 mg/m2), consisted of sensory neuropathy (3 patients), stomatitis (2 patients), and superficial keratopathy (2 patients). The MTD was thus determined to be 300 mg/m2 (level 2). Pharmacokinetic analyses revealed paclitaxel C(max) and area under the curve(inf) values to increase linearly over the ABI-007 dose range of 135-300 mg/m2. C(max) and area under the curve(inf) values for individual patients correlated well with toxicity.

Conclusions: ABI-007 offers several features of clinical interest, including rapid infusion rate, absence of requirement for premedication, and a high paclitaxel MTD. Our results provide support for Phase II trials to determine the antitumor activity of this drug.

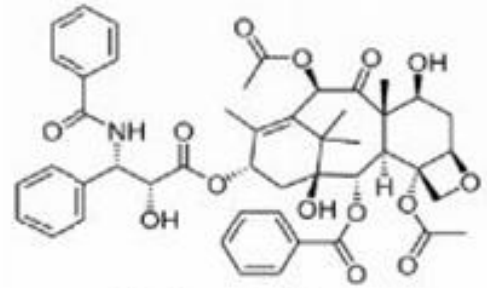
Results: Nineteen patients were treated. No acute hypersensitivity reactions were observed during the infusion period. Hematological toxicity was mild and not cumulative. Dose-limiting toxicity, which occurred in 3 of 6 patients treated at level 3 (375 mg/m2), consisted of sensory neuropathy (3 patients), stomatitis (2 patients), and superficial keratopathy (2 patients). The MTD was thus determined to be 300 mg/m2 (level 2). Pharmacokinetic analyses revealed paclitaxel C(max) and area under the curve(inf) values to increase linearly over the ABI-007 dose range of 135-300 mg/m2. C(max) and area under the curve(inf) values for individual patients correlated well with toxicity.

2005 to 2014: Low-Dose Metronomic at 100mg/m to Activate the Immune System

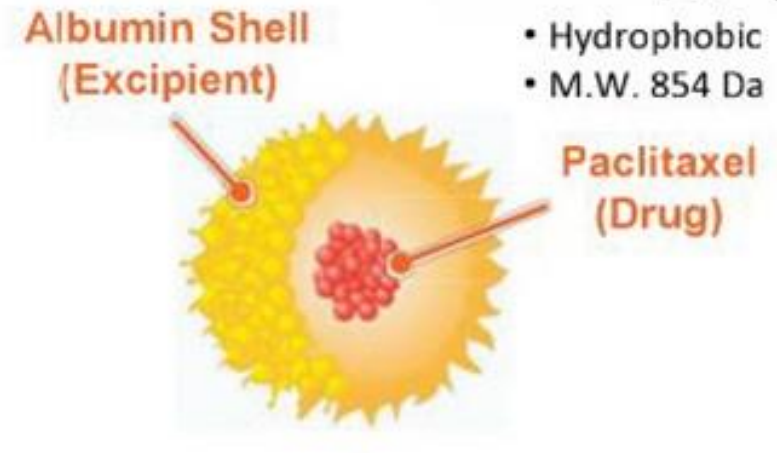
- Phase I 1998
- Breast Cancer 2005
- Lung Cancer 2012
- Pancreatic Cancer 2014

Abraxane®
for Injectable Suspension
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

Abraxis BioScience
* US FDA approved 2005

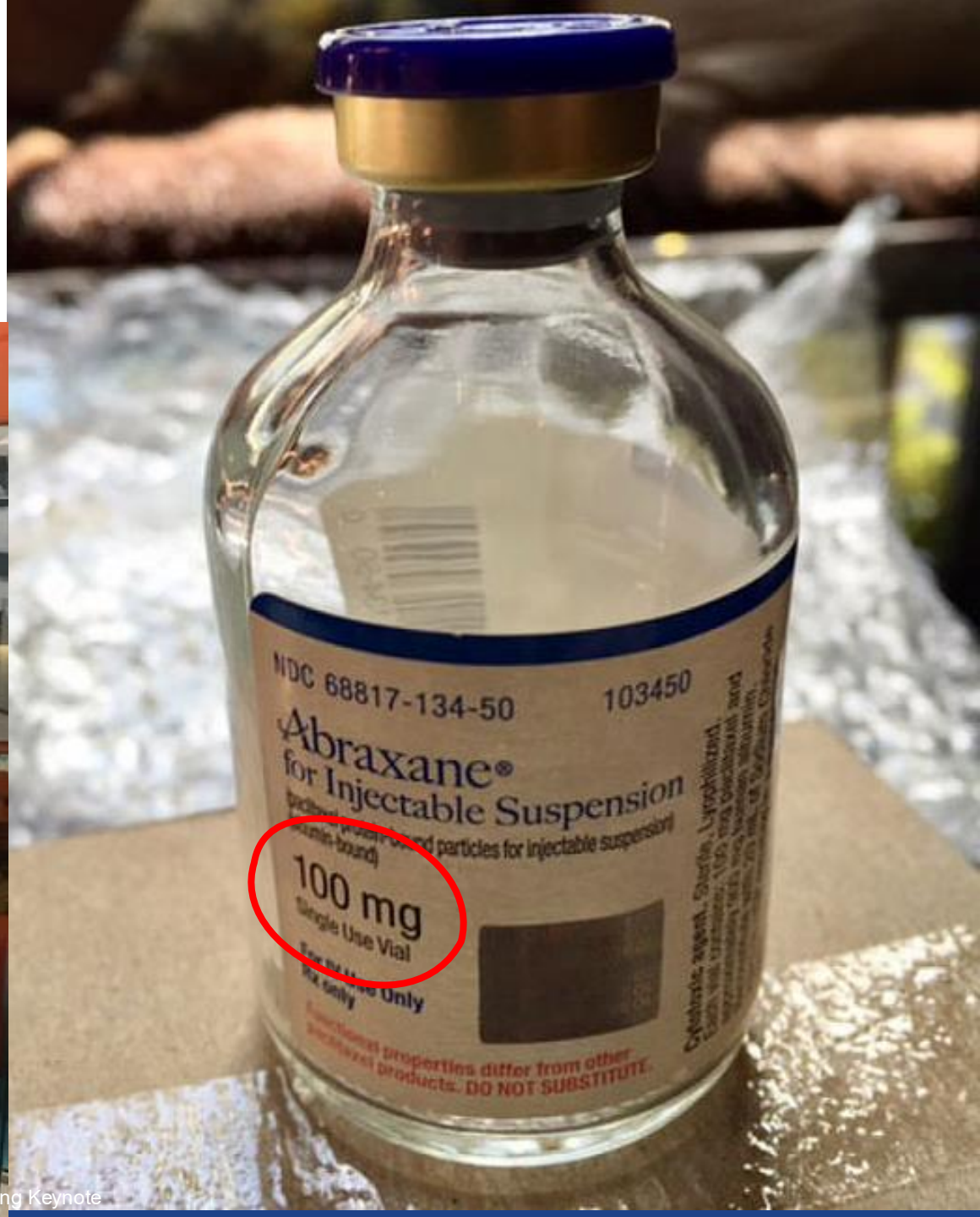


- Hydrophobic
- M.W. 854 Da



Smithsonian

NATIONAL MUSEUM OF AMERICAN HISTORY
BEHRING CENTER



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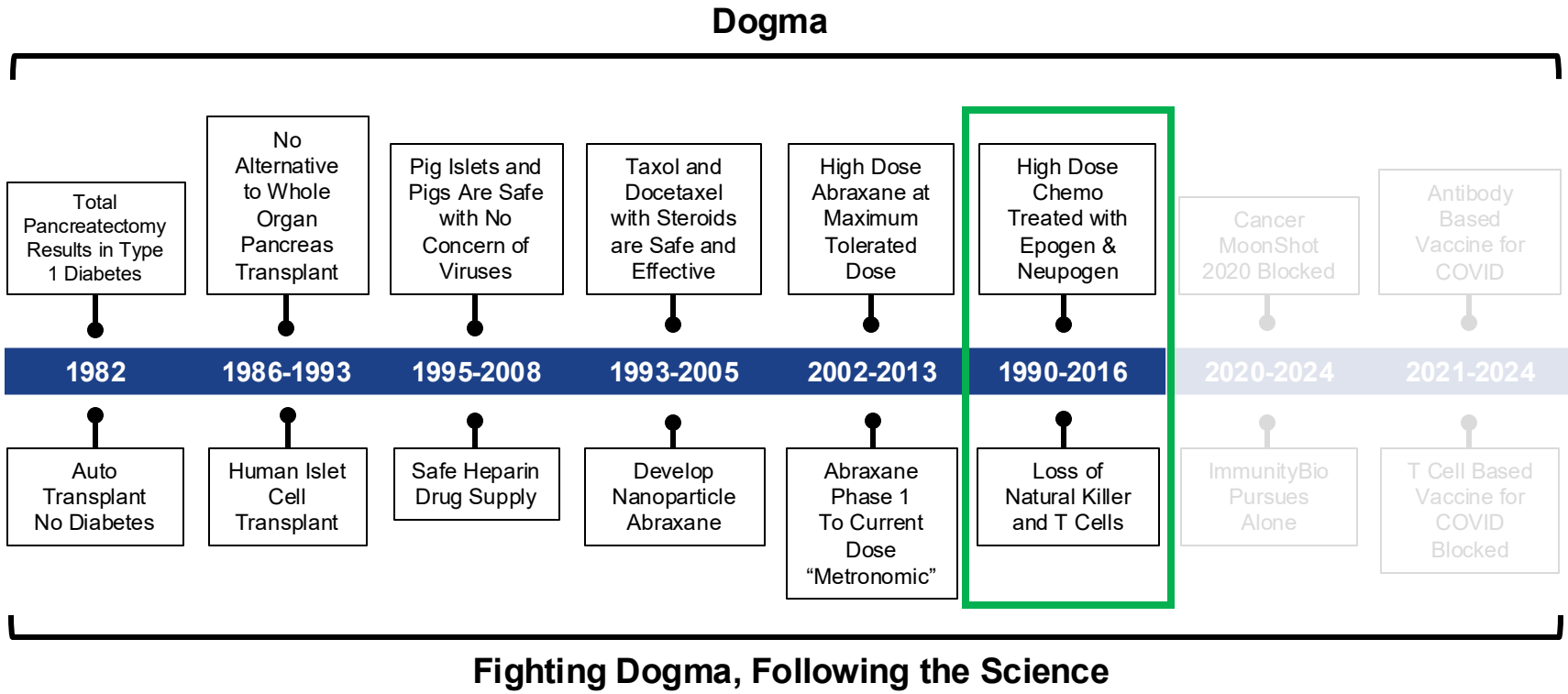


1990 – 2025: Follow the Science, The Power of the NK & T Cell to Fight Cancer (Lymphocytes)

> Horm Metab Res Suppl. 1990:25:215-9.

Prevention of CTL and NK cell-mediated cytotoxicity by microencapsulation

P Soon-Shiong [1], Z N Lu, I Grewal, R Lanza, W Clark

Affiliations + expand

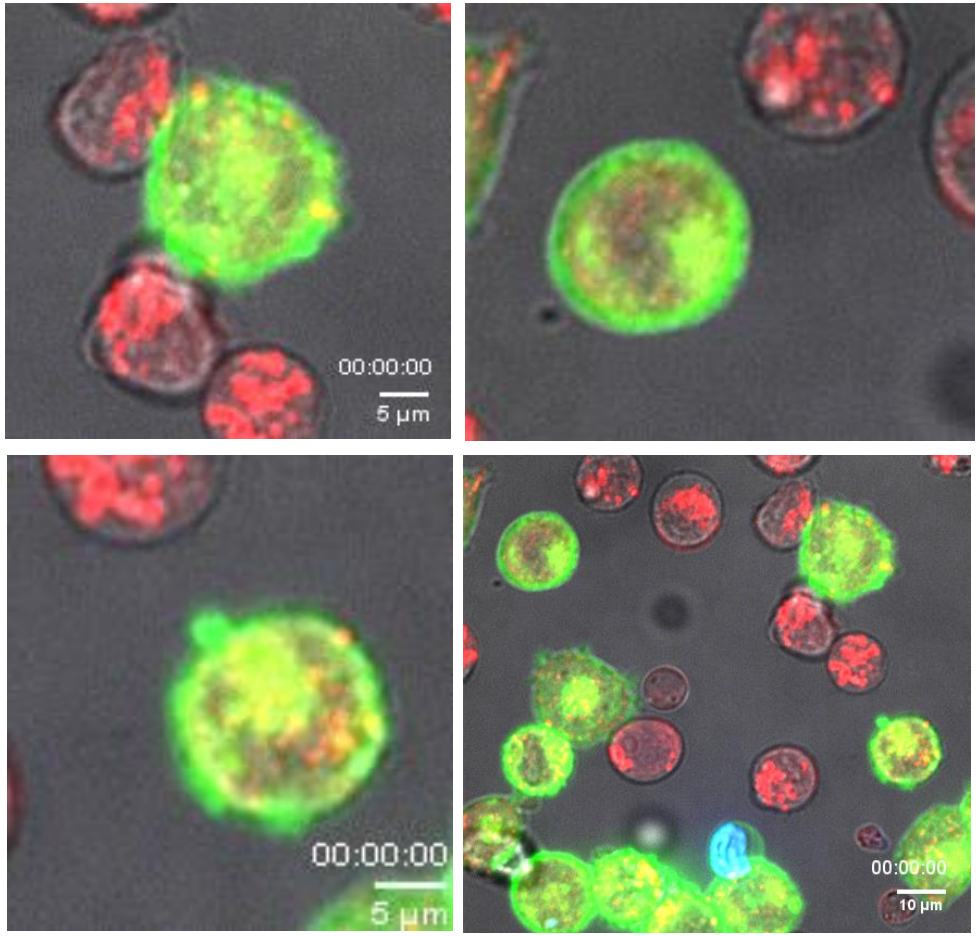
> Transplant Proc. 1990 Apr;22(2):754-5.

An in vitro method of assessing the immunoprotective properties of microcapsule membranes using pancreatic and tumor cell targets

P Soon-Shiong [1], Z N Lu, I Grewal, R P Lanza, W Clark

Affiliations + expand

PMID: 2327029



Red Lytic Granules in NK Cells (Cancer BioShield)
Green Live Breast Cancer Cells
Blue Dying Breast Cancer Cells

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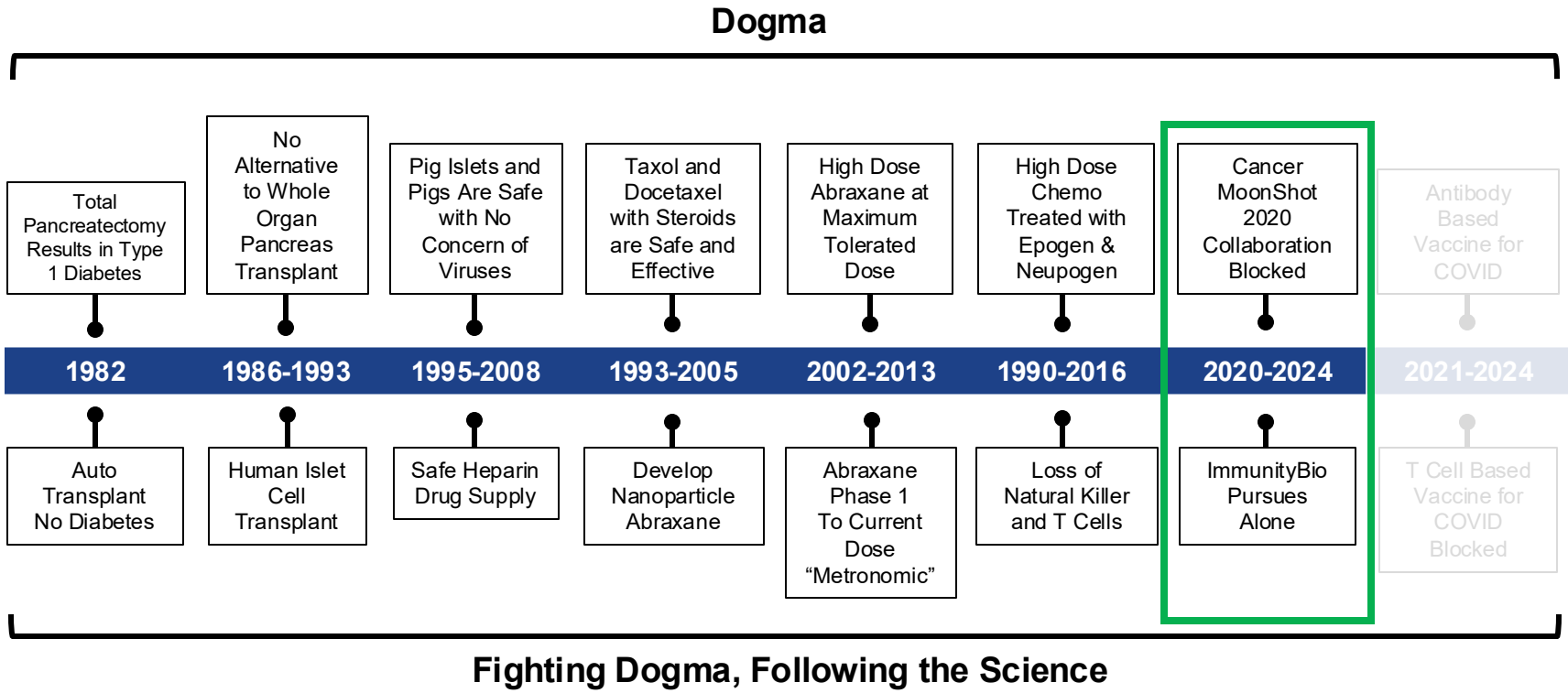


Dec 2015 – White House Visit

"The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, union of forces is necessary."

- William J. Mayo, M.D. (1910) Elder Son of Mayo, Surgeon

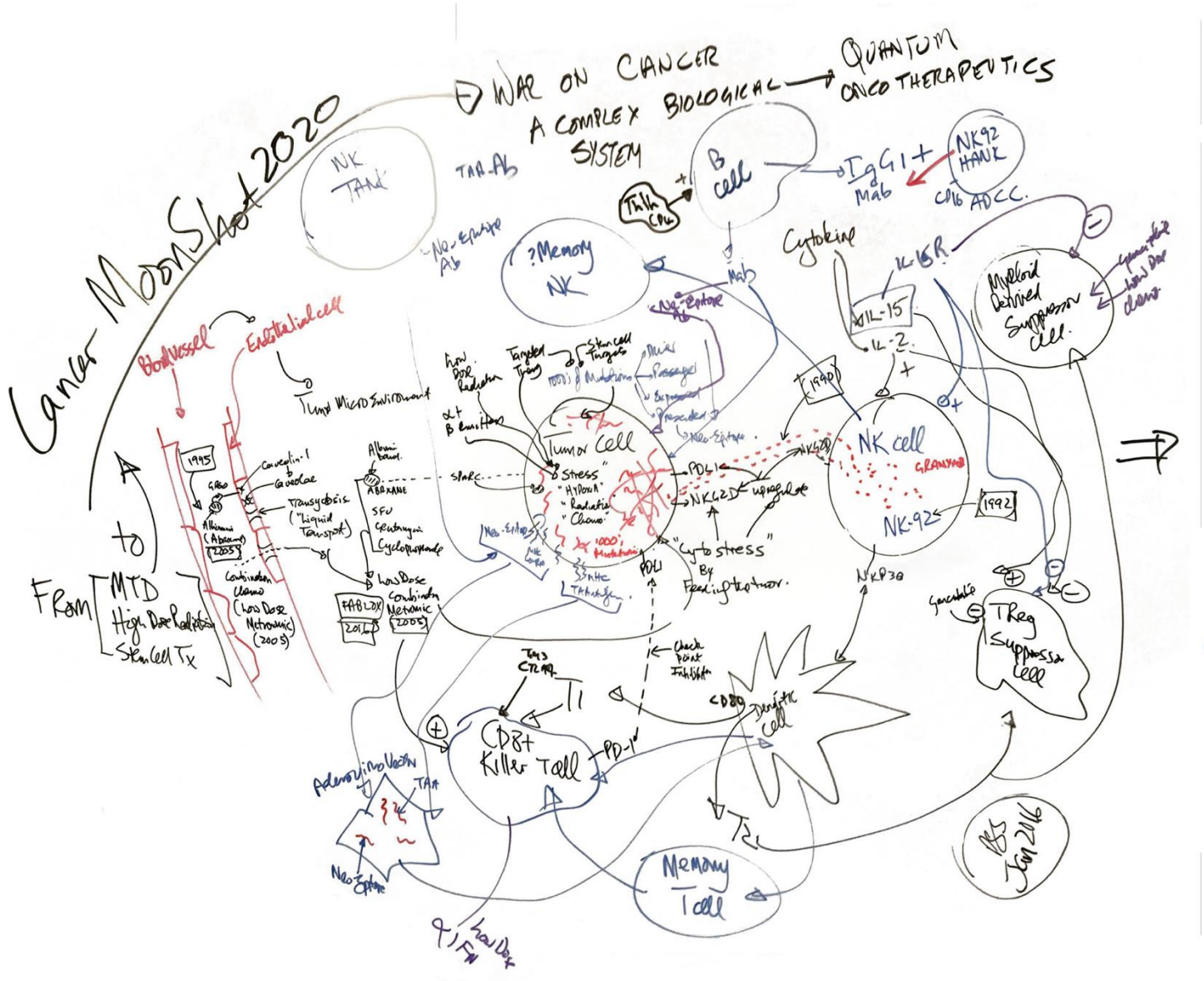
April 28-20, 2016 - Vatican – Pontifical Award

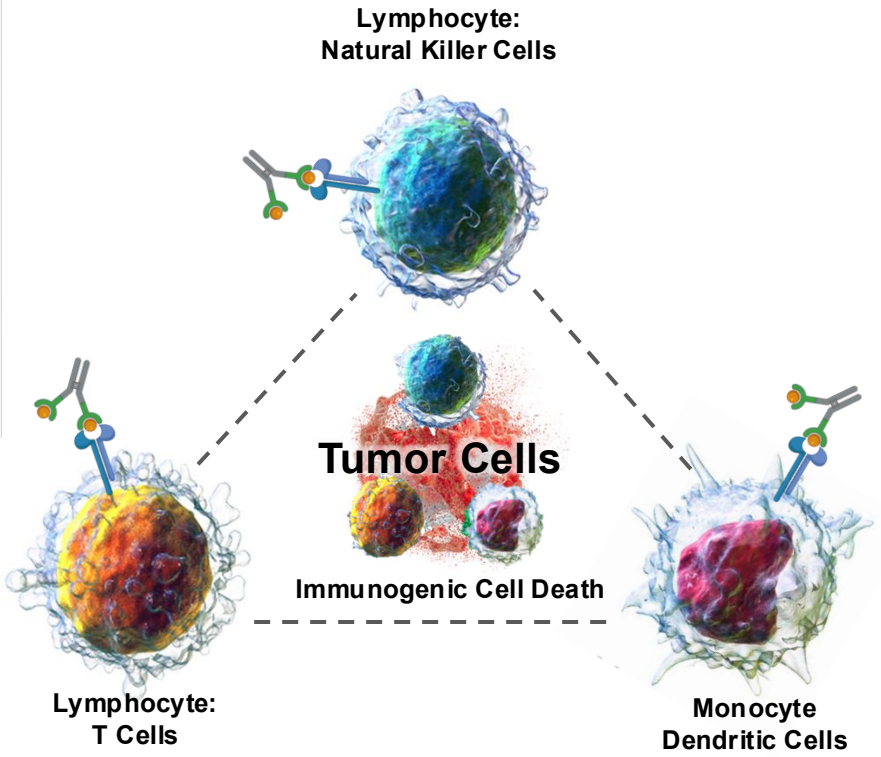
The Power of the Immune System (Natural Killer Cell)

The award, presented by His Eminence Gianfranco Cardinal Ravasi, President of the Pontifical Council for Culture, recognizes medical innovators who change the course of history and reduce suffering on a global scale by blending visionary thinking with real action.

"We congratulate Dr. Patrick Soon-Shiong, the recipient of the 2016 Key Visionary Award," said Cardinal Ravasi, President of the Pontifical Council For Culture. "In this Jubilee year of Mercy, **he gives hope to the many people suffering around the world that his vision and actions will lead to better medicine and a cure for cancer,** ushering in healing, hope and mercy for millions of people around the world."

2016: “Cancer MoonShot 2020”





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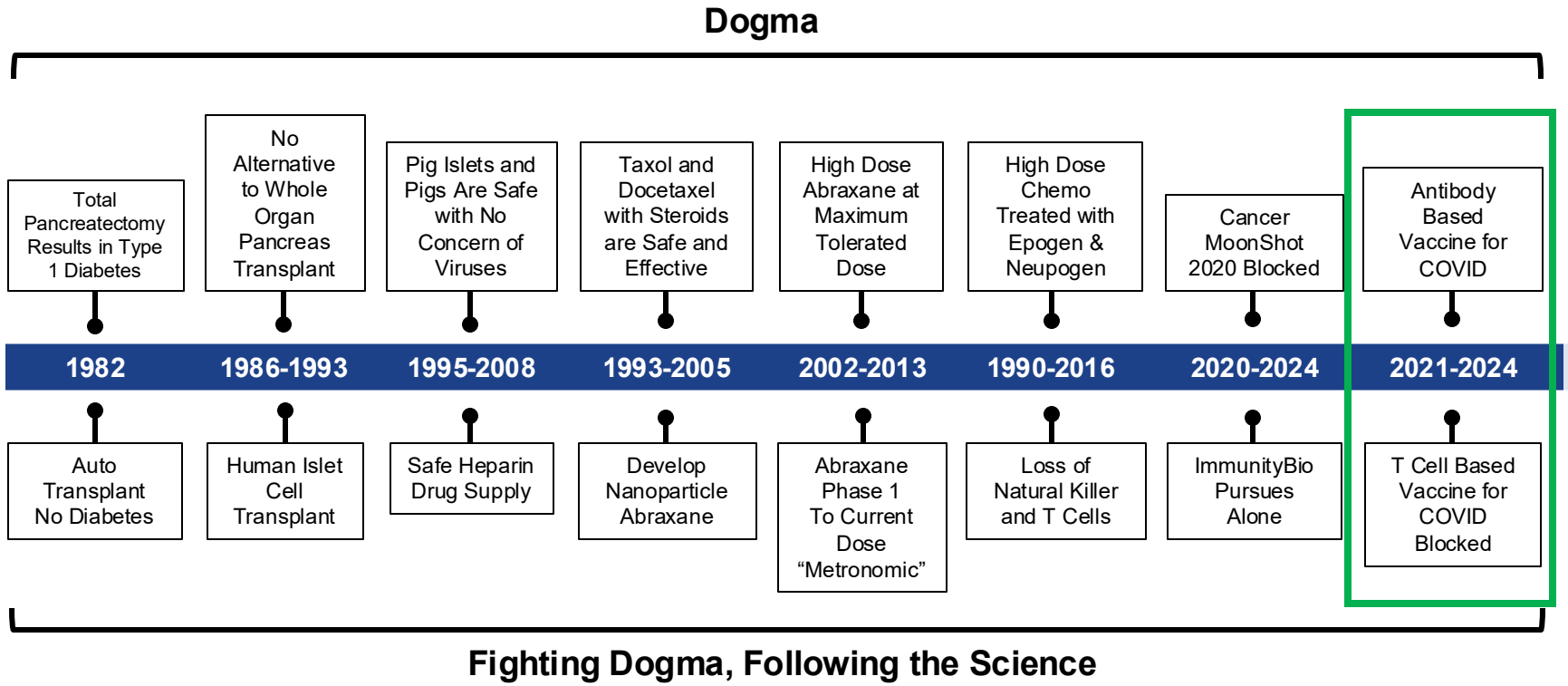

High Dose Chemo

Checkpoints

High Dose Radiation

Steroids

All Destroy the Very Cells Needed to Fight Cancer

Big Pharma Develops "Pre-Medication" Treatments to Treat the Adverse Events of those Treatments

Reduced Survival

Prolonged Survival

Preserve & Activate Lymphocytes to Prolong the Life of Cancer Patients without the Ravages of Standards of Care

The Cancer BioShield

Treat the Immune System of the Host

Natural Killer & T Cells

Use the Cancer Tissue In-Vivo as the Vaccine

Chemoradiation as Immunomodulators

July 2020: NANT T-Cell Based Vaccine Clears the Virus NIH/NIAID Controlled Non-Human Primate COVID Challenge Trial

Evaluating the Efficacy of Novel SARS-CoV-2 Vaccines in the NHP Model

Protocol

July 16, 2020

Study Number B05856

Biomedical Advanced Research & Development Authority (BARDA)
Office of the Assistant Secretary for Preparedness and Response (ASPR)
Department of Health and Human Services (DHHS)
330 Independence Avenue, SW, #644G
Washington, DC 20201

GLP Compliance Status: non-GLP

Battelle Biomedical Research Center
1425 Plain City-Georgesville Road
West Jefferson, Ohio 43162

BATTELLE

frontiers in Immunology

ORIGINAL RESEARCH
published: 16 September 2021
doi: 10.3389/fimmu.2021.729837

Dual-Antigen COVID-19 Vaccine Subcutaneous Prime Delivery With Oral Boosts Protects NHP Against SARS-CoV-2 Challenge

*Elizabeth Gabitzsch[1], Jeffrey T. Safrit[1], Mohit Verma[1], Adrian Rice[1], Peter Sieling[1], Lise Zakin[1], Annie Shin[1], Brett Morimoto[1], Helty Adisetiyo[1], Raymond Wong[1], Ashish Bezawada[1], Kyle Dinkins[1], Joseph Balint[1], Victor Peykov[1], Hermes Garban[1], Philip Liu[1], Andrew Bacon[3], Pete Bone[3], Jeff Drew[3], Daniel C. Sanford[4], Patricia Spilman[1], Lennie Sender[2], Shahrooz Rabizadeh[1], Kayvan Niazi[1] and Patrick Soon-Shiong[1]**

[1] ImmunityBio, Inc., Culver City, CA, United States, [2] NantKwest, Inc., Culver City, CA, United States, [3] IosBio, Burgess Hill, United Kingdom, [4] Battelle Biomedical Research Center, Columbus, OH, United States

OPEN ACCESS

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***Correspondence:**
Patrick Soon-Shiong
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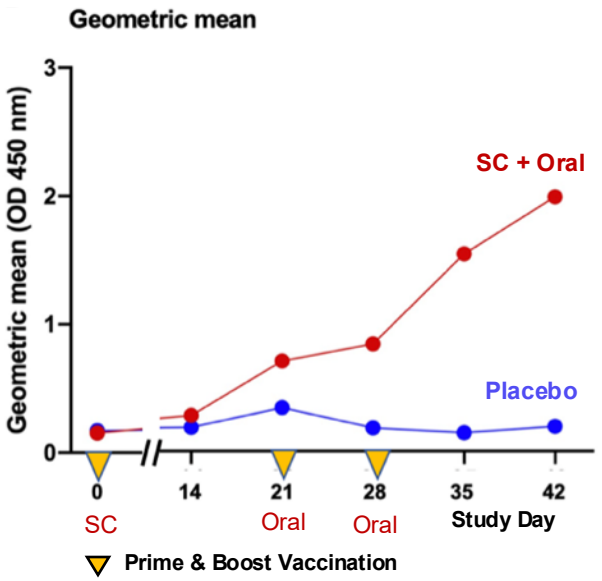
Specialty section:
This article was submitted to Vaccines and Molecular Therapeutics, a section of the journal Frontiers in Immunology

We have developed a dual-antigen COVID-19 vaccine incorporating genes for a modified SARS-CoV-2 spike protein (S-Fusion) and the viral nucleocapsid (N) protein with an Enhanced T-cell Stimulation Domain (N-ETSD) to increase the potential for MHC class II responses. The vaccine antigens are delivered by a human adenovirus serotype 5 platform, hAd5 [E1-, E2b-, E3-], previously demonstrated to be effective in the presence of Ad immunity. Vaccination of rhesus macaques with the hAd5 S-Fusion + N-ETSD vaccine by subcutaneous prime injection followed by two oral boosts elicited neutralizing anti-S IgG and T helper cell 1-biased T-cell responses to both S and N that protected the upper and lower respiratory tracts from high titer (1 x 10^6 $TCID_{50}$) SARS-CoV-2 challenge. Notably, viral replication was inhibited within 24 hours of challenge in both lung and nasal passages, becoming undetectable within 7 days post-challenge.

2020: T Cell Vaccine: NHP Challenge Study Operation Warp Speed

Antibodies

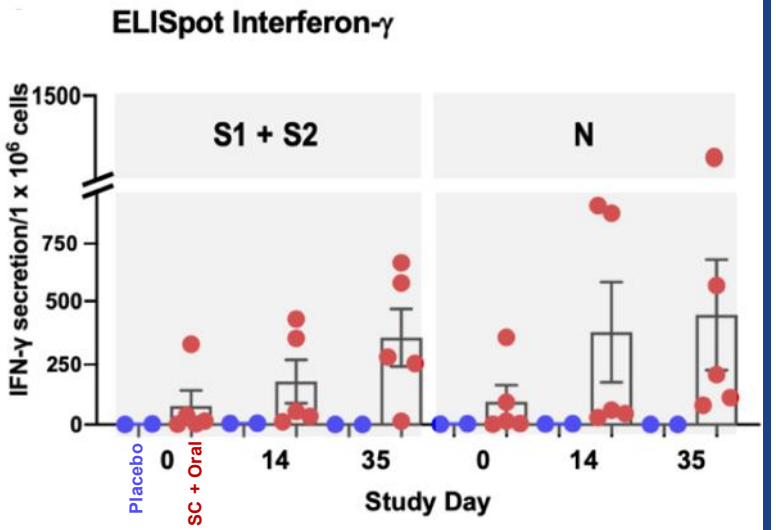
Anti-Spike IgG levels rise sharply after oral dosing



+

T cells

Induction of memory T cell ($CD4^+$) response to both antigens



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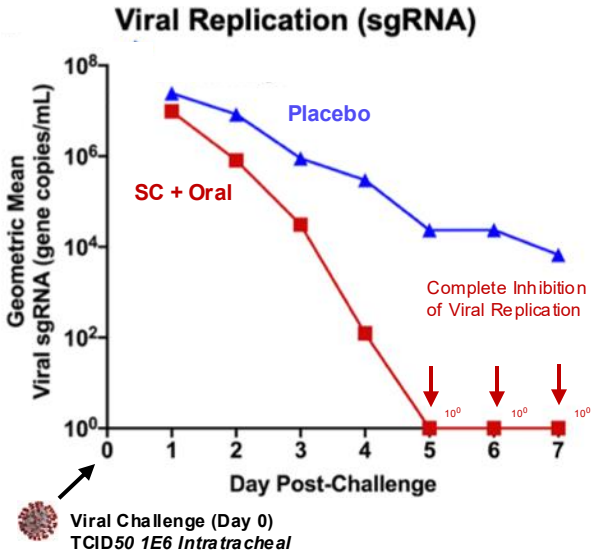
Protection

Rapid clearance of SARS-CoV-2 from nasal and airway tissue



Gabitzsch E, *et al.*, (2020) https://doi.org/10.1101/2020.12.08.416297

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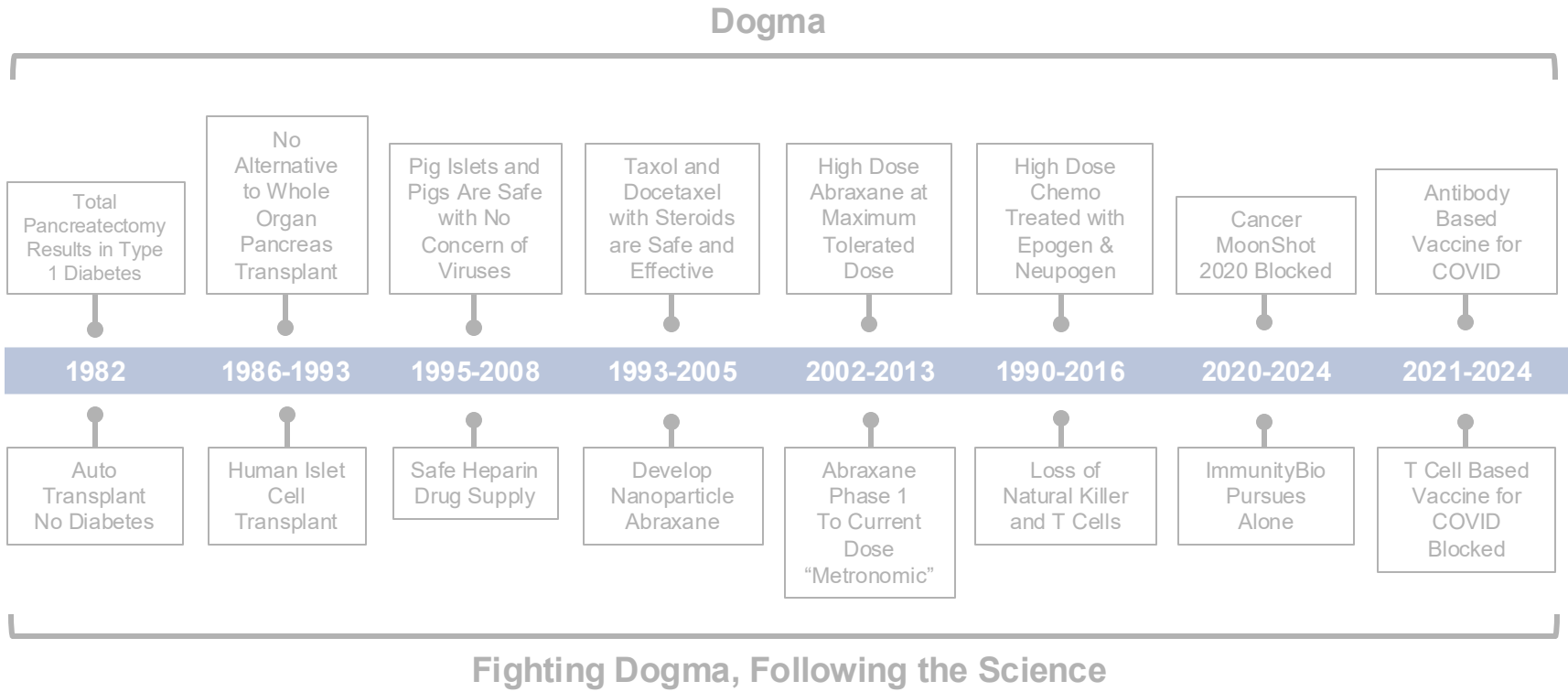
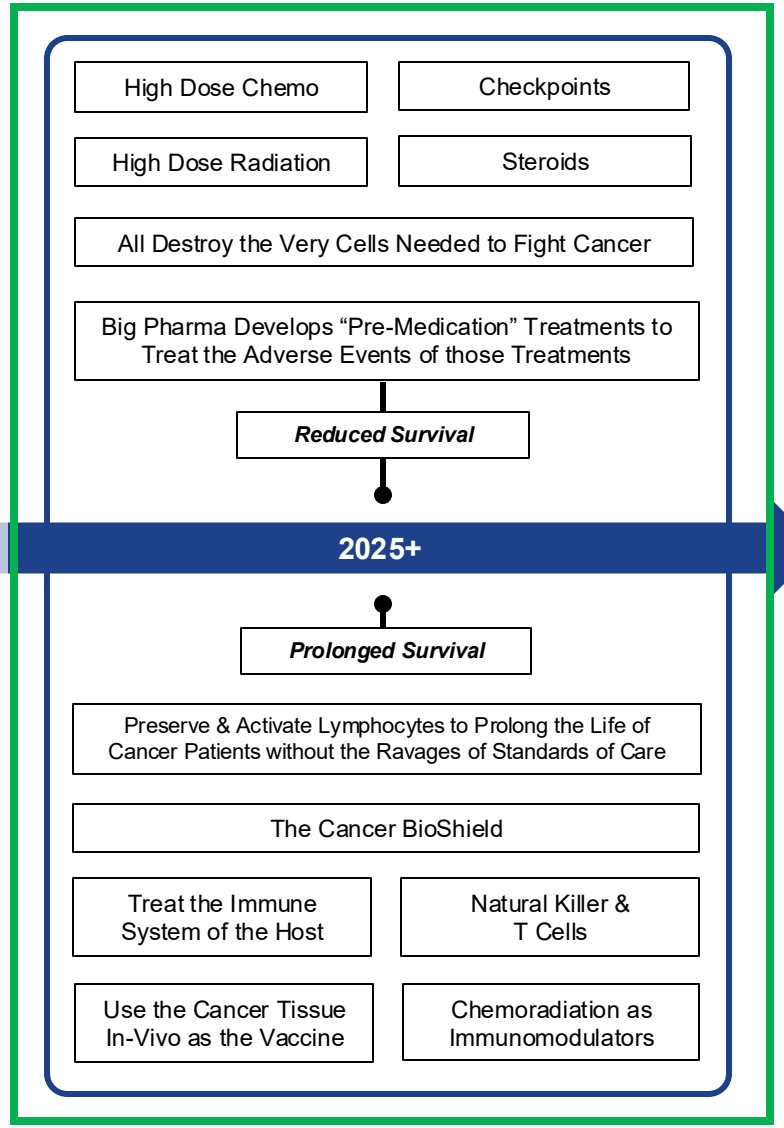
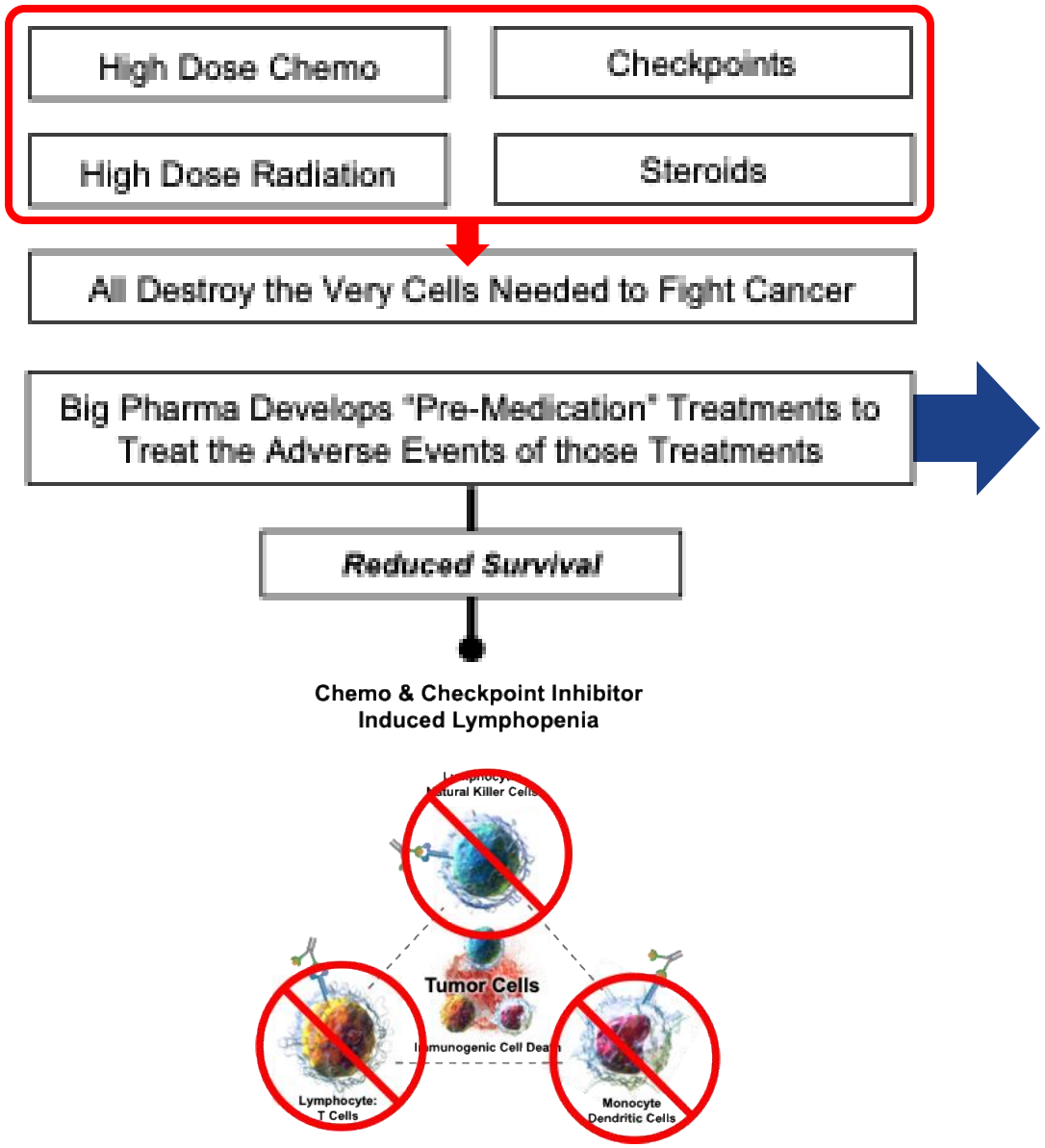




The Vicious Cycle of Standard of Care: The Missing Link, Lymphopenia



Premedications for Cancer Therapies: A Primer for the Hematology/Oncology Provider

AMBER CLEMMONS,[1,2] PharmD, BCOP, ARPITA GANDHI,[3] PharmD, BCOP, ANDREA CLARKE,[2] PharmD, SARAH JIMENEZ,[2] APN-BC, AGACNP, AOCNP®, THUY LE,[2] MD, and GERMAME AJEBO,[2] MD

From [1]University of Georgia College of Pharmacy, Augusta, Georgia; [2]Augusta University Medical Center, Augusta, Georgia; [3]Emory Healthcare, Atlanta, Georgia

Authors' disclosures of conflicts of interest are found at the end of this article.

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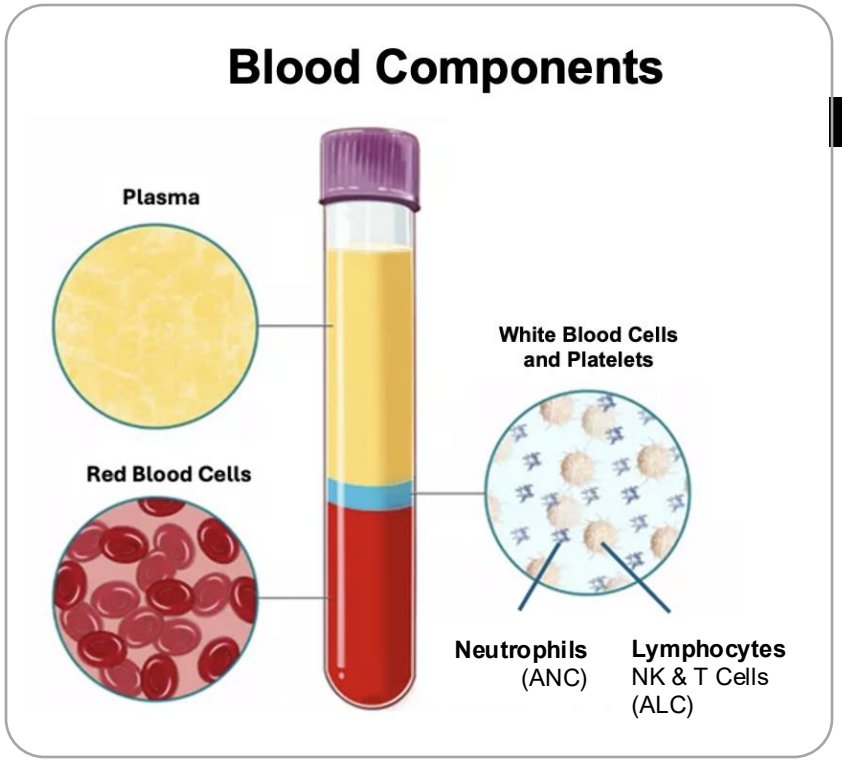
https://doi.org/10.6004/jadpro.2021.12.8.4

Abstract

Chemotherapeutic agents and radiation therapy are associated with numerous potential adverse events (AEs). Many of these common AEs, namely chemotherapy- or radiation-induced nausea and vomiting, hypersensitivity reactions, and edema, can lead to deleterious outcomes (such as treatment nonadherence or cessation, or poor clinical outcomes) if not prevented appropriately. The occurrence and severity of these AEs can be prevented with the correct prescribing of prophylactic medications, often called "premedications." The advanced practitioner in hematology/oncology should have a good understanding of which chemotherapeutic agents are known to place patients at risk for these adverse events as well as be able to determine appropriate prophylactic medications to employ in the prevention of these adverse events. While several guidelines and literature exist regarding best practices for prophylaxis strategies, differences among guidelines and quality of data should be explored in order to accurately implement patient-specific recommendations. Herein, we review the existing literature for prophylaxis and summarize best practices.

Introducing Absolute Lymphocyte Count (ALC) and Lymphopenia



ANC: Absolute Neutrophil Count
ALC: Absolute Lymphocyte Count

Red Blood Cell

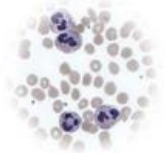
Low Red Blood Count

Anemia

EPOGEN

Treats Anemia
Increases Red Blood Cell Production
1989

Neutrophils



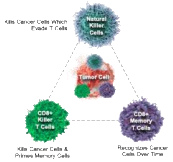
Low Neutrophil Count

Neutropenia

NEUPOGEN

Prevents Infection
Increases Neutrophil Production
1991

NK & T Cells



Low Lymphocyte Count

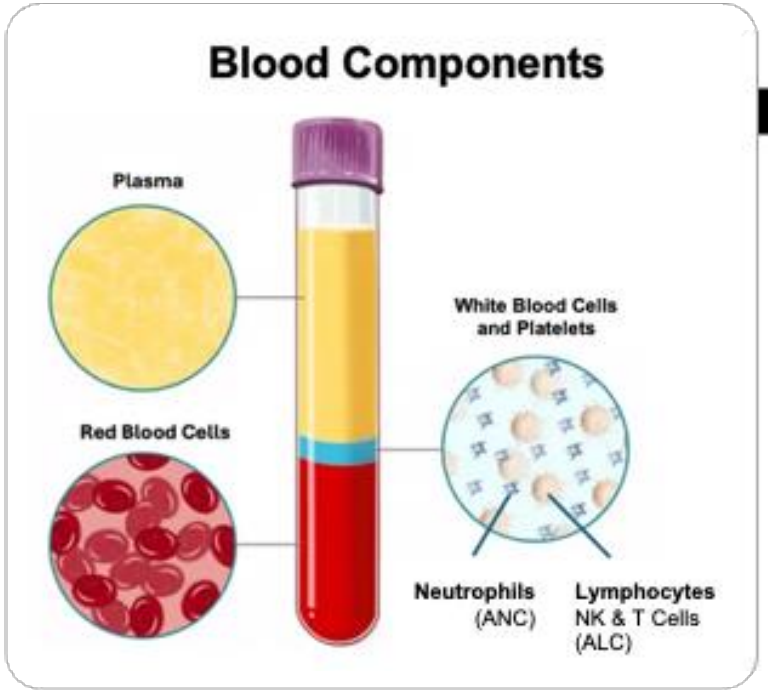
Lymphopenia

Loss of NK & T Cells
Which Kill Cancer &
Induce T Cell Memory

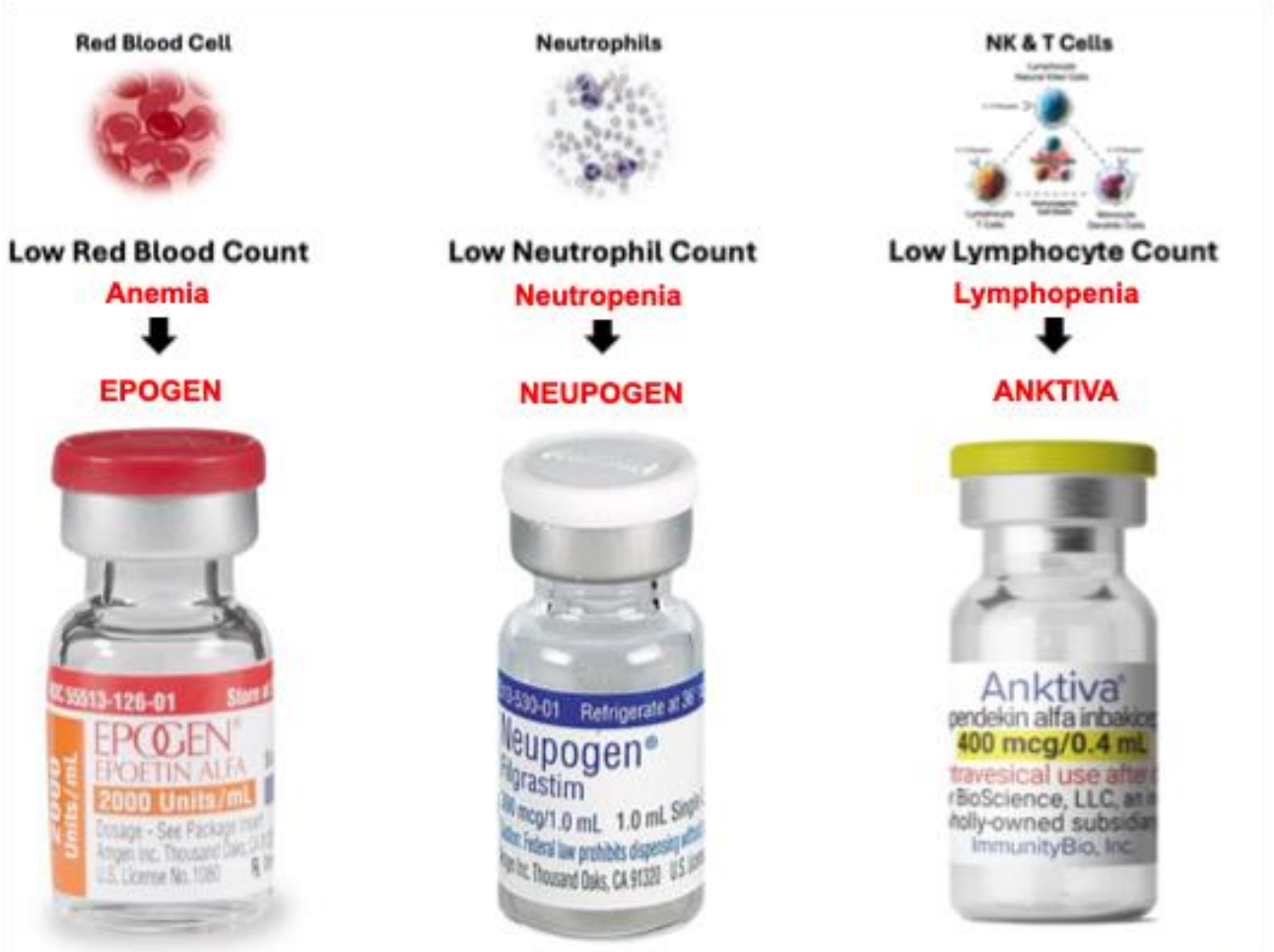
No Treatment for Over 50 Years
The Missing Link

Kills Cancer & Infected Cells

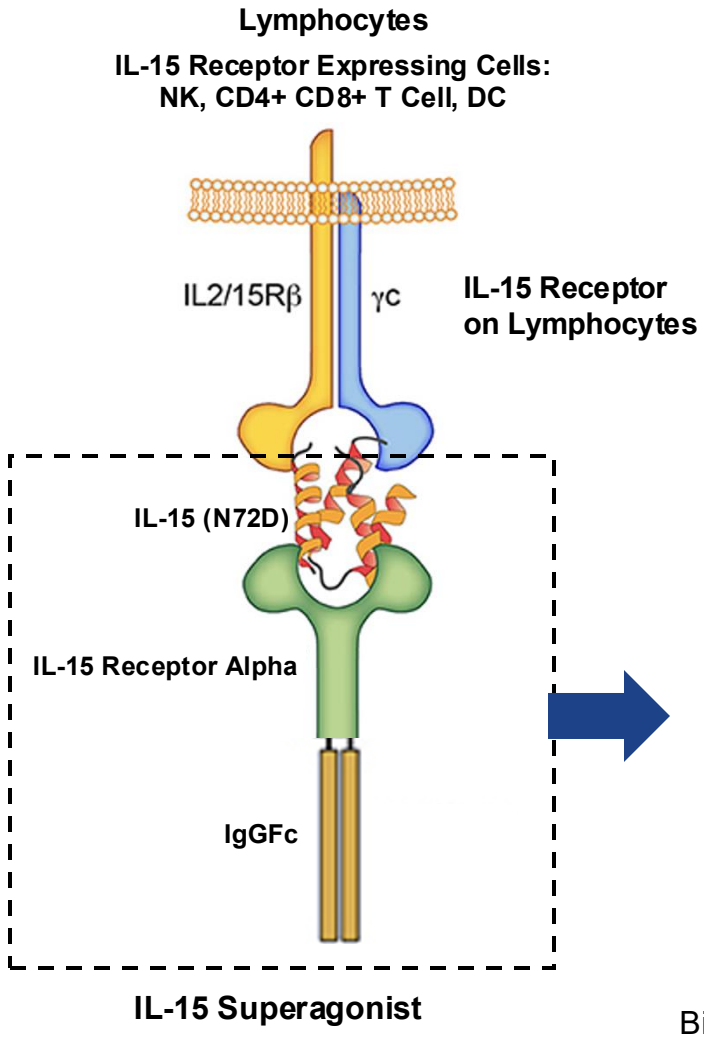
2024: First Lymphocyte Rescue Agent in 50+ Years as Backbone to Chemo-Immunotherapy and Radiotherapy



ANC: Absolute Neutrophil Count
ALC: Absolute Lymphocyte Count



April 2024: ANKTIVA FDA Approved Mechanism of Action

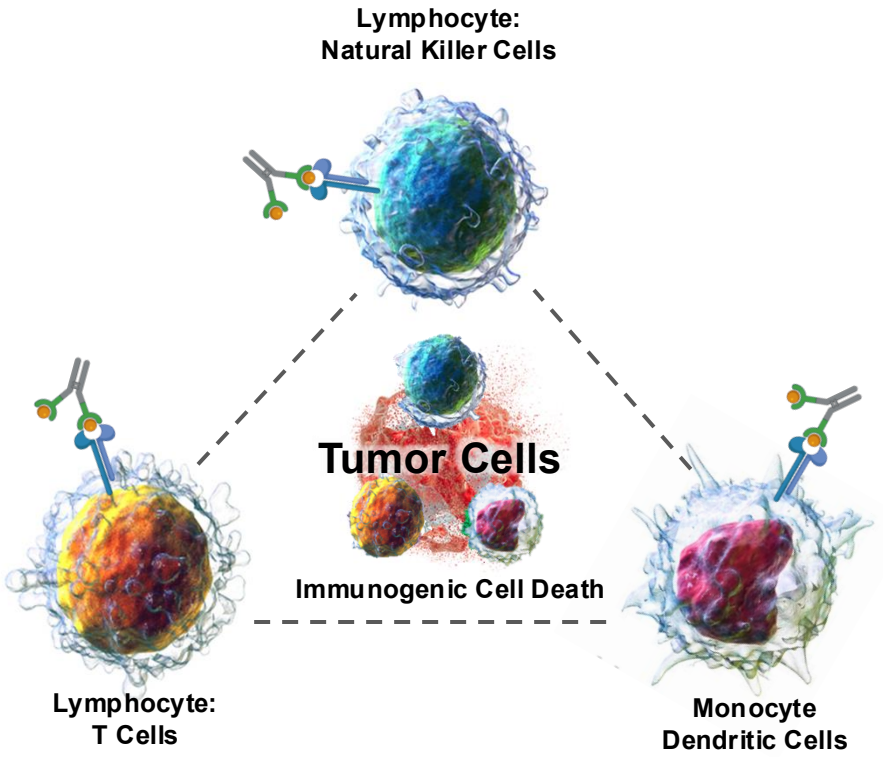


The Missing Link

Nogapendekin alfa inbakicept (NAI)

Lymphocyte Stimulating Agent

Binding of nogapendekin alfa inbakicept-pmln to its receptor results in proliferation and activation of NK, CD8+, and memory T cells without proliferation of immuno-suppressive Treg cells.

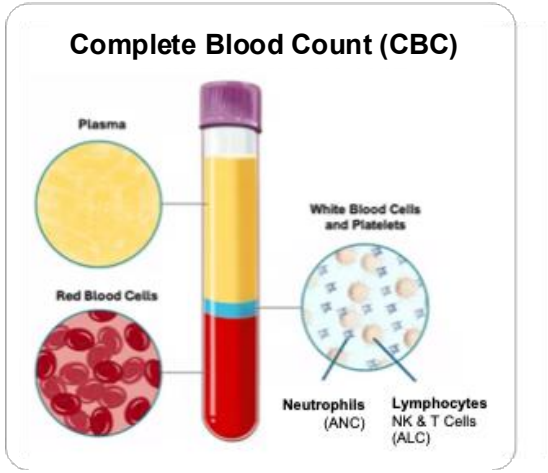


2025 to 2030: Fighting Dogma

The Power of the Immune System in Urology and All Cancers

High Immunosuppressive Neutrophil Count + **Low Lymphocyte Count** = **Recurrence & Low Overall Survival**

(High) **Absolute Neutrophil Count** **ANC** + (Low) **Absolute Lymphocyte Count** **ALC** = $\frac{\textbf{High ANC}}{\textbf{Low ALC}}$ = **High Neutrophil Lymphocyte Ratio**



The Barrier to the Cure

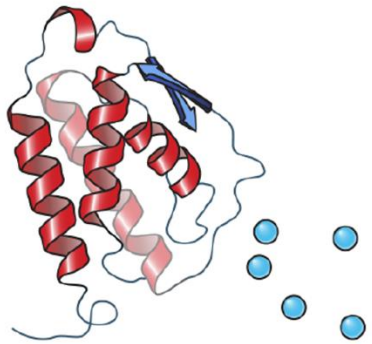
2025 to 2030: Fighting Dogma

The Power of the Immune System in Urology and All Cancers

Overcoming the Barriers to the Cure

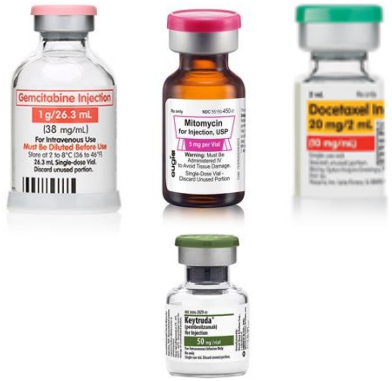
High Immunosuppressive Neutrophil Count + **Low Lymphocyte Count** = **Recurrence & Low Overall Survival**

(High) **Absolute Neutrophil Count** **ANC** + (Low) **Absolute Lymphocyte Count** **ALC** = **High ANC / Low ALC** = **High Neutrophil Lymphocyte Ratio**



GM-CSF

+

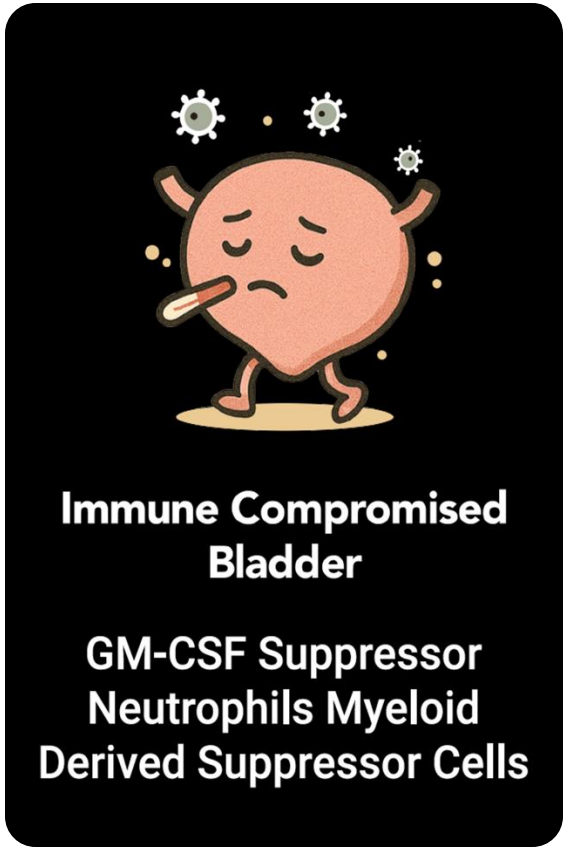


Chemotherapies & CPIs

=

Win the Battle…
Lose the War

Immunosuppressive Neutrophils Induced by GM-CSF



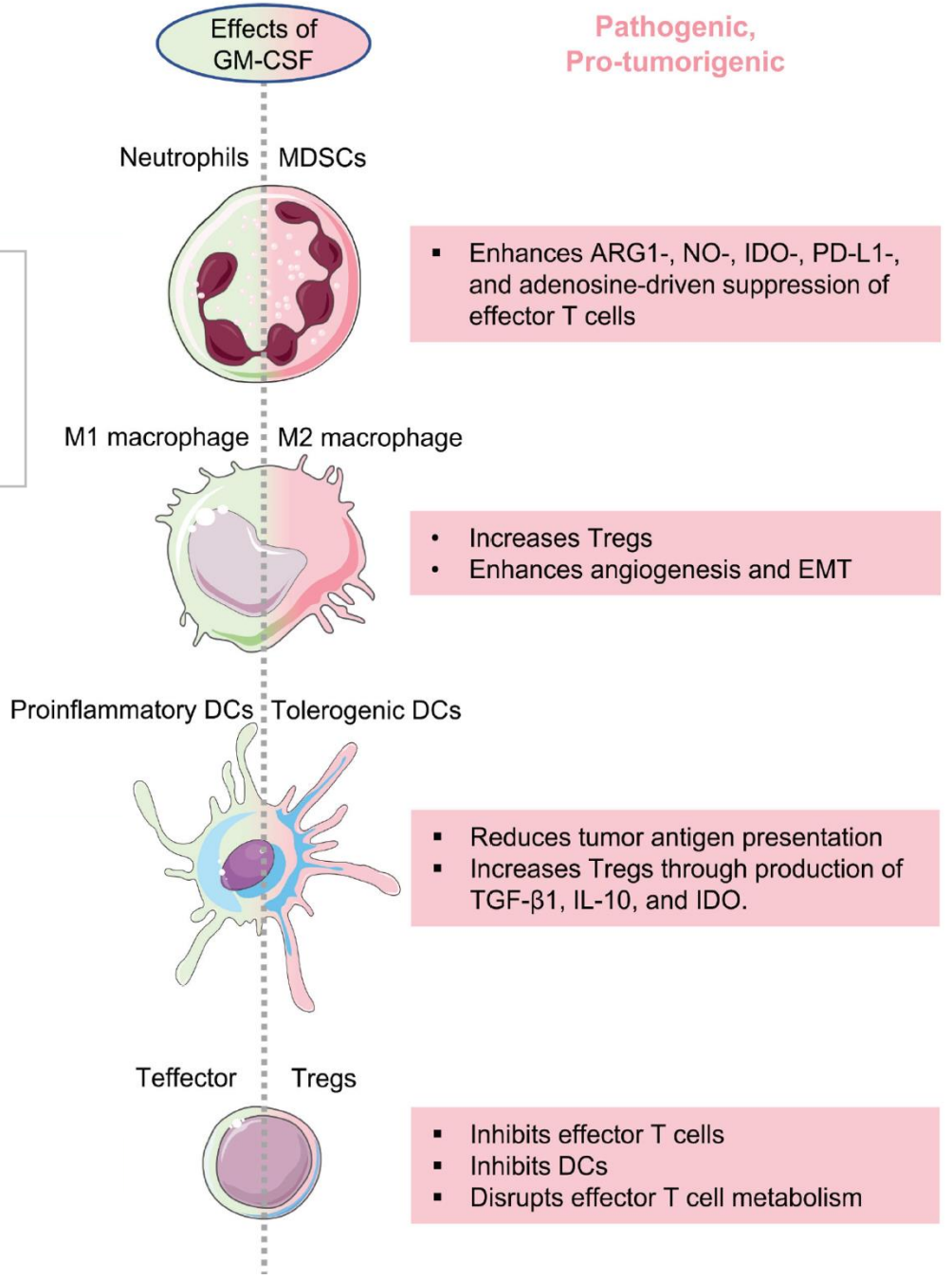
frontiers | Frontiers in Immunology
REVIEW
published: 05 July 2022
doi: 10.3389/fimmu.2022.901277

GM-CSF: A Double-Edged Sword in Cancer Immunotherapy

*Anil Kumar[1], Adeleh Taghi Khani[1], Ashly Sanchez Ortiz[1] and Srividya Swaminathan[1,2]**

The Dynamic Quantum State of the Immune System:
From initial response to long-term tumor evasion

"Win the battle… lose the war."



Immunosuppressive Neutrophils Induced by GM-CSF

Review

trd Tuberculosis & Respiratory Diseases

Immune Evasion of G-CSF and GM-CSF in Lung Cancer

https://doi.org/10.4046/trd.2023.0037
ISSN: 1738-3536(Print)/ 2005-6184(Online)
Tuberc Respir Dis 2024;87:22-30

Yeonhee Park, M.D., Ph.D.[1] and Chaeuk Chung, M.D., Ph.D.[2,3]

frontiers | Frontiers in Immunology

REVIEW
published: 05 July 2022
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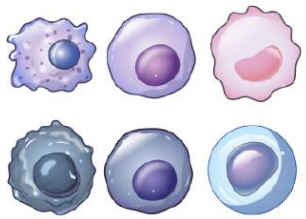
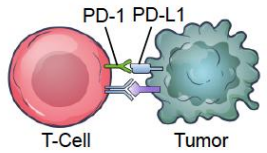
GM-CSF: A Double-Edged Sword in Cancer Immunotherapy

*Anil Kumar[1], Adeleh Taghi Khani[1], Ashly Sanchez Ortiz[1] and Srividya Swaminathan[1,2]**



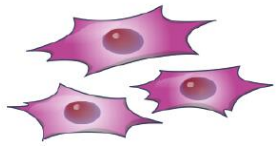
[Immune cells]

Induce Necroptosis
Inhibit T cell, NK cell
Activate MDSC, Treg cell,
M2 macrophage



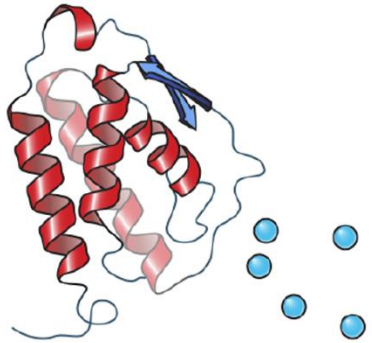
[PD-L1 activation]

Immune suppression
Promote EMT, invasion, metastasis

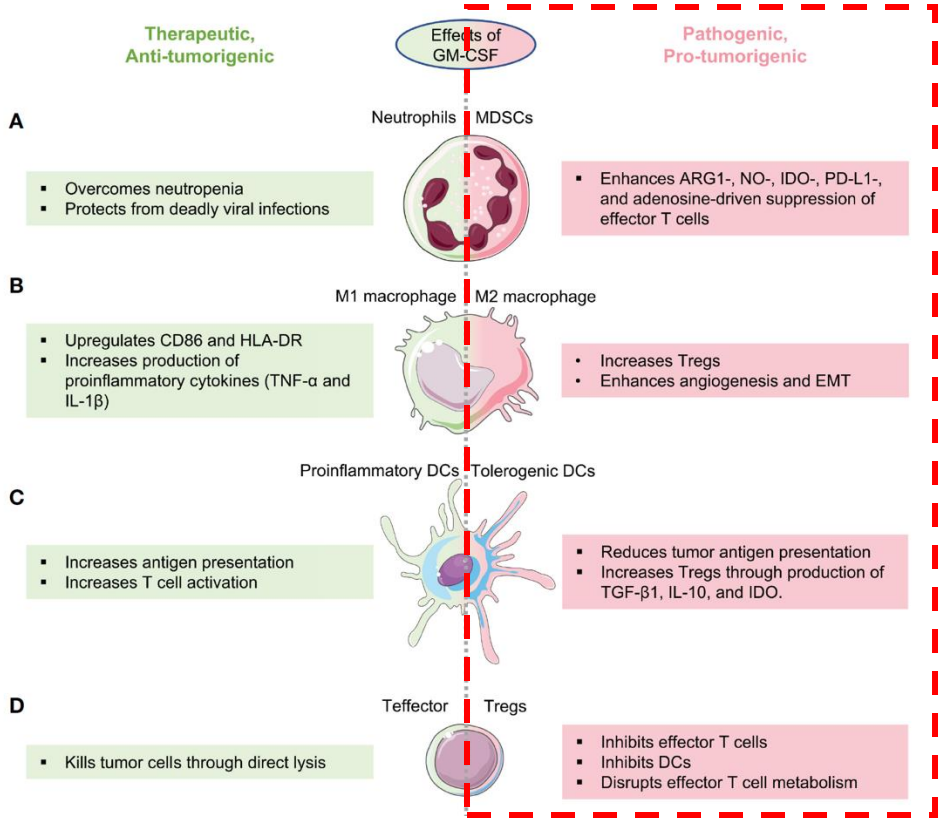


[Cancer cells]

Increase the invasive capacity
Enhance extracellular matrix-degrading proteinases



GM-CSF



"Win the battle… lose the war."

High Neutrophil to Lymphocyte Ratio Results in Early Recurrence

Getzler *et al. BMC Urology* (2018) 18:90
https://doi.org/10.1186/s12894-018-0404-x

BMC Urology

RESEARCH ARTICLE Open Access

Preoperative neutrophil to lymphocyte ratio improves recurrence prediction of non-muscle invasive bladder cancer

Itamar Getzler[1*†], Zaher Bahouth[1†], Ofer Nativ[1], Jacob Rubinstein[2] and Sarel Halachmi[1]

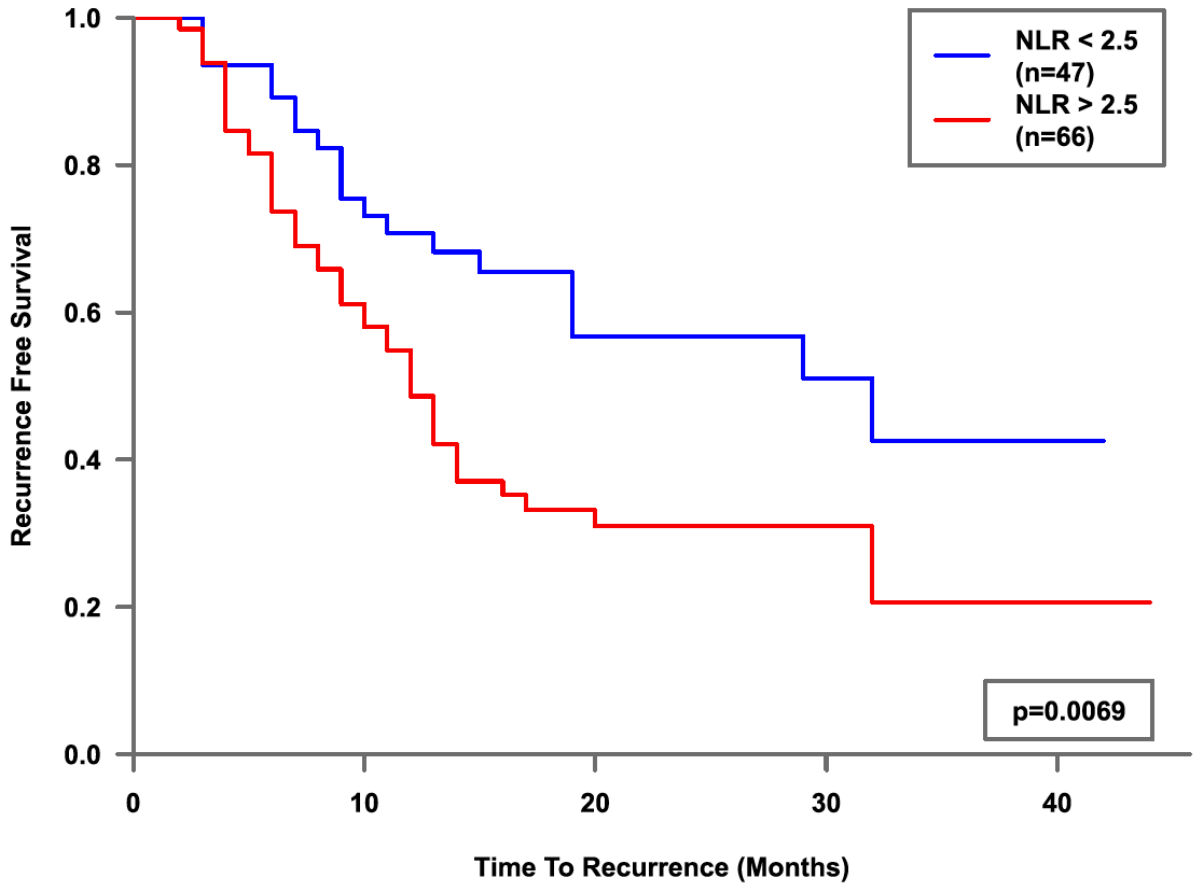
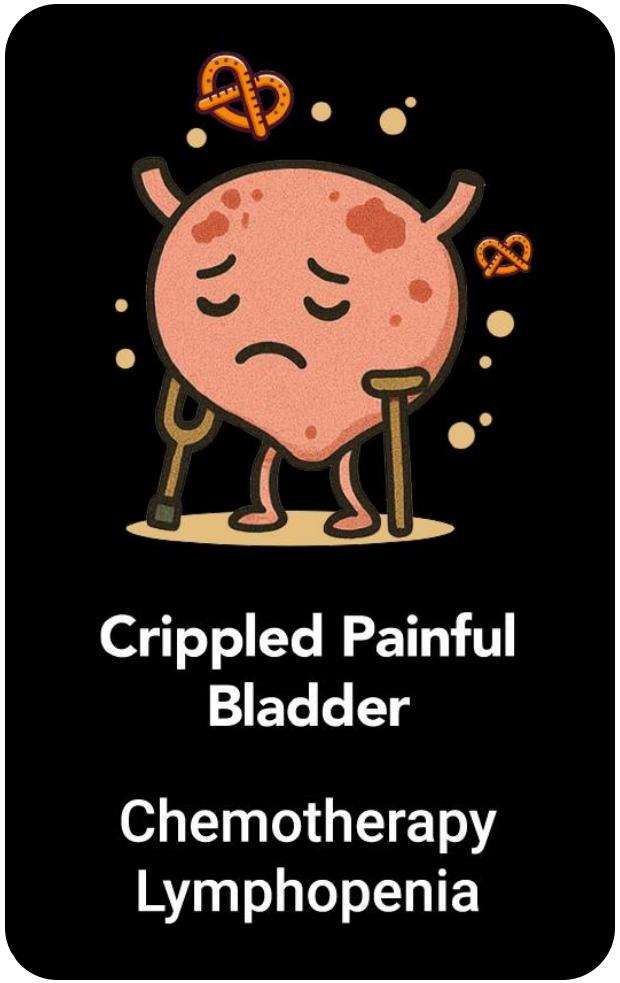


Fig. 1 Kaplan-Meier estimates of recurrence-free survival factored by NLR 2.5 - whole cohort analysis

High Immunosuppressive Neutrophil Count + Low Lymphocyte Count = High NLR Ratio = Recurrence

Chemotherapy & CPI Induced Lymphopenia



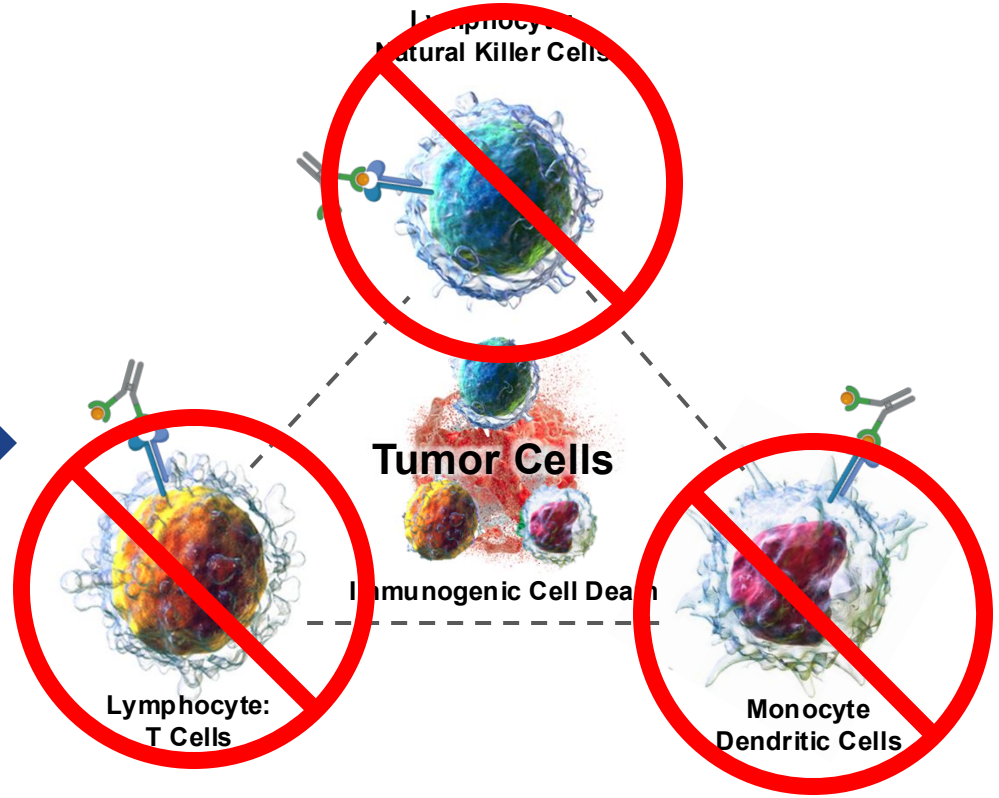
Lymphocyte Depleting Agents

Absolute Lymphocyte Count (ALC) Ignored for 50 Years

Chemotherapies

Checkpoint Inhibitors

Chemo & Checkpoint Inhibitor Induced Lymphopenia



"Win the battle… Lose the war."

The Barrier to the Cure
Chemotherapy Induced Lymphopenia

Published in final edited form as:
Cancer Res. 2009 July 1; 69(13): 5383–5391. doi:10.1158/0008-5472.CAN-08-3845.

LYMPHOPENIA AS A PROGNOSTIC FACTOR FOR OVERALL SURVIVAL IN ADVANCED CARCINOMAS, SARCOMAS AND LYMPHOMAS

Isabelle Ray-Coquard[1], Claire Cropet[2], Martine Van Glabbeke[3], Catherine Sebban, MD[1], Axel Le Cesne[4], Ian Judson[5], Olivier Tredan[1], Jaap Verweij[6], Pierre Biron[1], Inthidar Labidi[1], Jean-Paul Guastalla[1], Thomas Bachelot[1], David Perol[2], Sylvie Chabaud[2], Pancras C.W. Hogendoorn[7], Philippe Cassier[8], Armelle Dufresne[8], and Jean-Yves Blay[8,9] on behalf of the EORTC Soft Tissue and Bone Sarcoma Group

blood®
Volume 84, Issue 7, 1 October 1994, Pages 2221-2228

Article

Lymphocyte Depletion During Treatment With Intensive Chemotherapy for Cancer

Crystal L. Mackall, Thomas A. Fleisher, Margaret R. Brown, Ian T. Magrath, Aziza T. Shad, Marc E. Horowitz, Leonard H. Wexler, Melissa A. Adde, Linda L. McClure, Ronald E. Gress

The Barrier to the Cure
Checkpoint Induced Lymphopenia

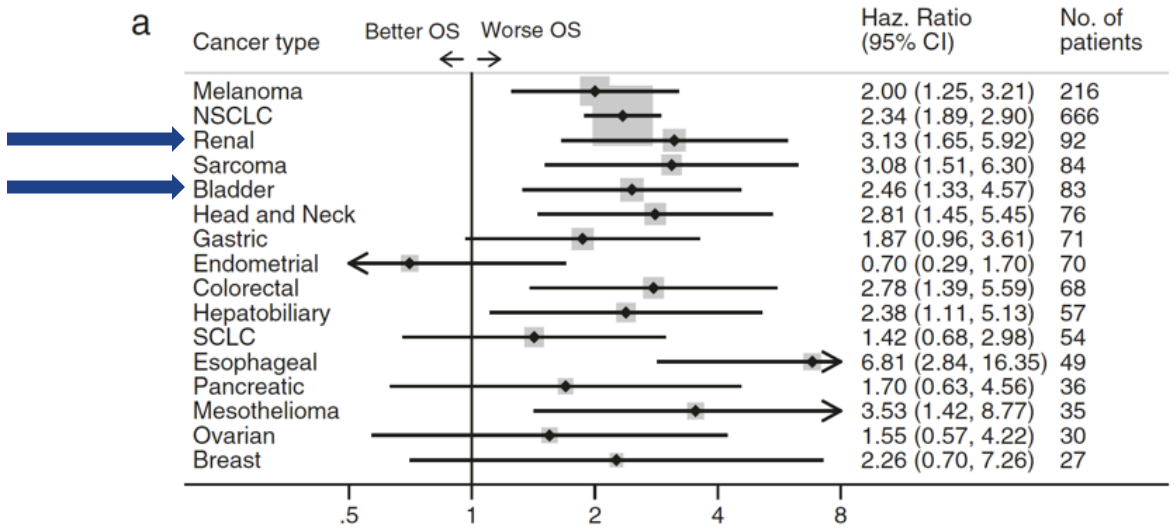
nature COMMUNICATIONS

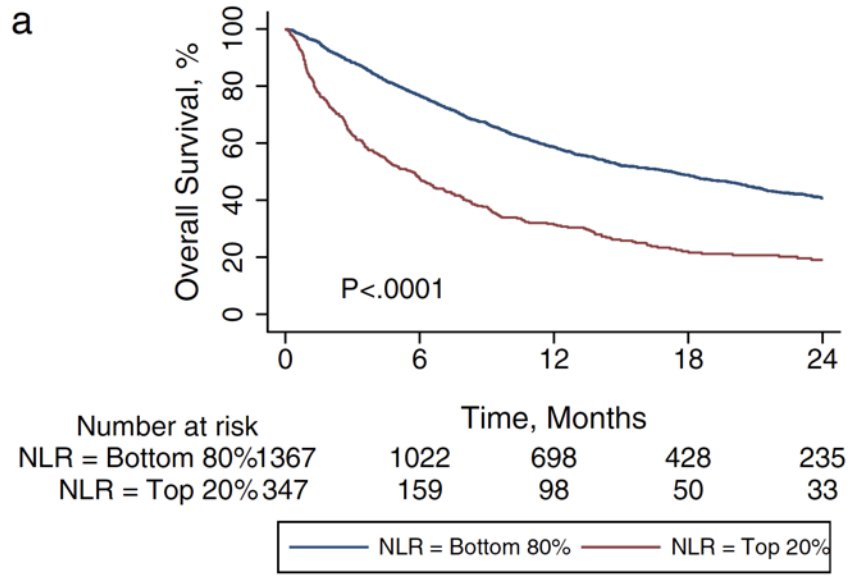
ARTICLE

https://doi.org/10.1038/s41467-021-20935-9 OPEN

Pretreatment neutrophil-to-lymphocyte ratio and mutational burden as biomarkers of tumor response to immune checkpoint inhibitors

Cristina Valero[1,2,3], Mark Lee[2,3], Douglas Hoen[2,3], Kate Weiss[2,3], Daniel W. Kelly[4], Prasad S. Adusumilli[1], Paul K. Paik[5], George Plitas[1], Marc Ladanyi[6], Michael A. Postow[5], Charlotte E. Ariyan[1], Alexander N. Shoushtari[5], Vinod P. Balachandran[1], A. Ari Hakimi[1,2,3], Aimee M. Crago[1], Kara C. Long Roche[1], J. Joshua Smith[1], Ian Ganly[1,2,3], Richard J. Wong[1], Snehal G. Patel[1], Jatin P. Shah[1], Nancy Y. Lee[7], Nadeem Riaz[2,3,7], Jingming Wang[2,3], Ahmet Zehir[6], Michael F. Berger[6], Timothy A. Chan[2,3,7,9]✉, Venkatraman E. Seshan[8,9]✉ & Luc G. T. Morris[1,2,3,9]✉





Lymphopenia Associated with Significant Lower OS (p=0.006)

2024

ARTICLE OPEN

Check for updates

Exploring the prognostic impact of absolute lymphocyte count in patients treated with immune-checkpoint inhibitors

M. R. Conroy[1,2], H. O'Sullivan[1,2], D. C. Collins[1,2], R. M. Bambury[1,2], D. Power[1,2,3], S. Grossman[4] and S. O'Reilly[1,2,3]✉

BACKGROUND: The role of immune checkpoint inhibitors (ICI) expands but affordable and reproducible prognostic biomarkers are needed. We investigated the association between baseline and 3-month absolute lymphocyte count (ALC) and survival for patients on ICI.
METHODS: A retrospective study investigated patients who received ICI July 2014—August 2019. Survival probabilities were calculated for lymphocyte subsets. Univariate and multivariate analyses were performed to investigate risk factors for lymphopenia.
RESULTS: Among 179 patients, median age was 62 and 41% were female. The most common diagnoses were melanoma (41%) and lung cancer (40%). Median PFS was 6.5 months. 27% had baseline lymphopenia (ALC < 1×10^9cells/L) and no significant difference in PFS or OS to those with normal ALC. However, 31% had lymphopenia at 3 months and significantly shorter OS than those without (9.8 vs 18.3 months, $p < 0.001$). Those with baseline lymphopenia who recovered counts at 3 months had no difference in PFS (median NR vs 13.0 months, $p = 0.48$) or OS (22 vs 18.3 months, $p = 0.548$) to those never lymphopenic. The strongest risk factor for lymphopenia on multivariable analysis was previous radiation therapy (RT).
CONCLUSIONS: 3-month lymphopenia is a negative prognostic marker in cancer patients on ICI. Previous RT is significantly associated with lymphopenia.

BJC Reports; https://doi.org/10.1038/s44276-024-00058-6

When analysis was limited to those with lymphopenia grade 3 and 4 (<0.5×10^9cells/L), there were similar findings to all-grade lymphopenia. Those with severe lymphopenia at baseline had no significant difference in PFS compared to those without, but those with severe lymphopenia at 3 months had significantly shorter PFS than those without (3.6 vs 10.9 months, $p = 0.026$). This was further explored with a Cox regression analysis incorporating presence of severe lymphopenia as a time-dependent covariate. This found that the difference in PFS did not reach statistical significance ($p = 0.214$) but the difference in OS was significant ($p = 0.006$). This difference in OS remained significant on multivariable analysis incorporating age, sex, histologic subtype, previous RT, previous SACT, ICI type and whether the patient had an irAE.

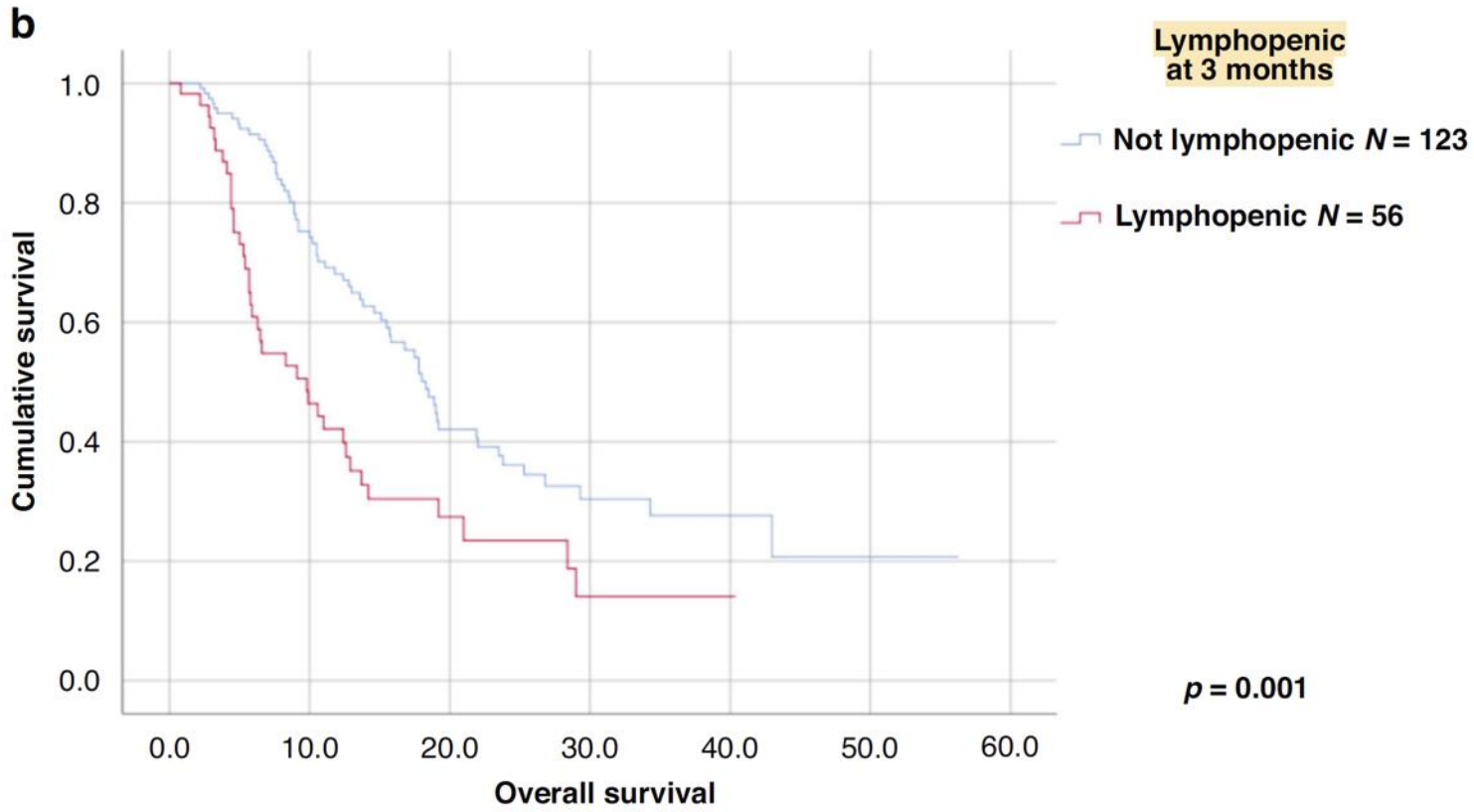


Table 1 Different published studies exploring the impact of the global lymphopenia or NK and T cell subsets on relapse-free survival (RFS) or overall survival (OS) in patients with solid tumors

From: Lymphopenia in Cancer Patients and its Effects on Response to Immunotherapy: an opportunity for combination with Cytokines?

Tumor Type	N	Type of lymphopenia evlauated	Lymphocyte Threshold (% lymphopenia)	RFS (Cox Analysis)			OS (Cox Analysis)			References
				RR	IC 95%	P value	RR	IC 95%	P value	
Sarcoma	193	Overall Lymphopenia	<1000 (24%)	Not evaluated			1.46	1.0-2.1	0.05	[68]
Ewing Sarcoma	24	Overall Lymphopenia	<500 (33%)	Not evaluated			4.34	1.35-14.28	0.007	[75]
Renal Cell Carcinoma	424	Overall Lymphopenia	≤1300 (28.06%)	Not evaluated			1.75	1.14-2.67	0.0102	[65]
Colon Carcinoma	260	Overall Lymphopenia	<1000 (19%)	1.56	1.0-2.43	0.048	2.35	2.34-4.14	0.003	[66]
Breast Carcinoma	195	Overall Lymphopenia	<1000 (28.7%)	1.82	1.27-2.59	0.001	2.23	1.36-3.65	0.001	[89]
Non Hodgkin Lymphoma	322	Overall Lymphopenia	<1000 (25%)	1.71	1.2-2.4	0.002	1.48	1.03-2.21	0.04	[68]
Diffuse large B cell lymphoma (DLBCL)	151	Overall Lymphopenia	≤1000 (35.8%)	Not evaluated			2.38	1.29-4.34	0.005	[90]
DLBCL	221	Overall Lymphopenia	<1000 (38.9%)	2.72	1.61-4.60	<0.001	2.51	1.38-4.58	0.003	[80]
DLBCL	89	Overall Lymphopenia	<840 (23%)	3.81	1.72-8.42	0.0009	4.38	1.88-13.28	0.0012	[79]
Follicular Lymphoma	228	Overall Lymphopenia	≤1000 (28%)	Not evaluated			1.72	1.33-2.24	$<10^{-4}$	[70]
Hodgkin Lymphoma	476	Overall Lymphopenia	<600 (18.06%)	1.59	0.96-2.58	0.06	1.25	0.74-2.15	0.4	[82]
Hodgkin Lymphoma	2497	Overall Lymphopenia	<600 (11%)	1.38		0.002	Not evaluated			[81]
Multiple Myeloma	537	Overall Lymphopenia	<1400 (62%)	Not evaluated			1.71	1.53-2.35	$<10^{-4}$	[92]
ATLL	60	Overall Lymphopenia	<1000 (35.6%)	1.93		0.004	2.37		0.0003	[93]
PTCLU	69	Overall Lymphopenia	<1000 (38%)	Not evaluated			4.0	1.9-8.3	$<10^{-4}$	[71]
PTCL-NOS	118	Overall Lymphopenia	1000 (30.5%)	1.94	1.19-3.18	0.008	2.24	1.33-3.78	0.002	[72]
Breast Carcinoma	287	Overall Lymphopenia	<1000 (27%)	1.48	1.1-2.0	0.01	1.8	1.3-2.4	0.0002	[68]
Breast Carcinoma	195	Overall Lymphopenia	<1000 (28.7%)	1.82	1.27-2.59	0.001	2.23	1.36-3.65	0.001	[89]
Breast Carcinoma 1st relapse	128	Overall Lymphopenia	<1000 (44.27%)	Not evaluated			1.8	1.15-2.82	0.01	[50][b]
Breast Carcinoma 1st relapse 1st relapse	103	Overall Lymphopenia	<700 (22.3%)	Not evaluated			2.03	1.17-3.50	0.016	[21][b]
Breast Carcinoma 1st relapse 1st relapse	103	$CD4^+$ Lymphopenia	≤450 (53.4%)	Not evaluated			2.50	1.57-3.98	$<10^{-4}$	[21][b]
Breast Carcinoma >2nd relapse	101	$CD4^+$ Lymphopenia	≤450 (70.3%)	1.35	0.87-1.1	0.183	1.69	1.04-2.78	0.036	[21]
Metastatic Solid Tumors	219	$CD4^+$ Lymphopenia	≤450 (47.9%)	Not evaluated			1.5	1.1-2.1	0.017	[20]
Metastatic Solid Tumors	213	$CD4^+$ Lymphopenia	<450 (49.7%)	Not evaluated			7.7[a]	1.6-35[a]	0.007[a]	[19][a]
Non Hodgkin Lymphoma	88	$CD8^+$ Lymphopenia	<200	Not evaluated			3.30	1.21-9.0	0.01	[88]
Follicular Lymphoma	75	NK cells Lymphopenia	<150 (44%)	Not evaluated			6.73	0.76-59	0.08	[69]
DLBCL	136	NK cells Lymphopenia	≤80 (37.5%)	1.81	1.27-2.57	0.001	Not evaluated			[94]

[a] Analysis of the risk of early death; [b] Univariate analysis only

2019

Ménétrier-Caux *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:85
https://doi.org/10.1186/s40425-019-0549-5

Journal for ImmunoTherapy of Cancer

REVIEW Open Access

Lymphopenia in Cancer Patients and its Effects on Response to Immunotherapy: an opportunity for combination with Cytokines?

Christine Ménétrier-Caux[1,2*], Isabelle Ray-Coquard[3], Jean-Yves Blay[1,3†] and Christophe Caux[1,2†]

Abstract

Quantitative lymphocyte alterations are frequent in patients with cancer, and strongly impact prognosis and survival. The development of cancers in immunosuppressed patients has demonstrated the contribution of different T cell populations, including $CD4^+$ cells, in the control of cancer occurrence.

Whereas absolute numbers of neutrophils, platelets and red blood cells are routinely monitored in clinic following treatments, because of possible short-term complications, absolute lymphocyte counts (ALC), their subpopulations or diversity (phenotype, TCR) are rarely analyzed and never used to choose therapy or as prognostic criteria. The recent identification of immune checkpoint inhibitors (ICPi) as powerful therapeutic agents has revitalized immunotherapy of cancer in a broader group of diseases than anticipated. The status of the immune system is now recognized as an important biomarker for response to these novel treatments. Blood ALC values, along with tumor infiltration by $CD8^+$T cells, and ICPi and ICPi-ligand expression, are likely to be a potential marker of sensitivity to anti-ICPi therapy.

In this article, we review the current knowledge on the incidence and significance of lymphopenia in cancer patients, and discuss therapeutic strategies to restore lymphocyte numbers.

Keywords: Lymphopenia, solid tumors, TCR diversity, anti-cancer immunotherapy

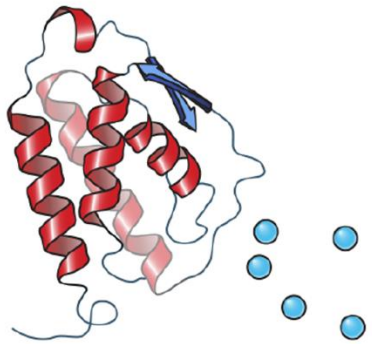
2025 to 2030: Fighting Dogma

The Power of the Immune System in Urology and All Cancers

Overcoming the Barriers to the Cure

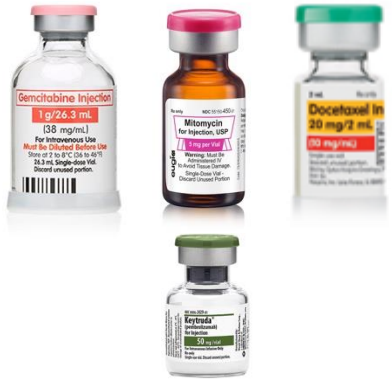
High Immunosuppressive Neutrophil Count + **Low Lymphocyte Count** = **Recurrence & Low Overall Survival**

(High) **Absolute Neutrophil Count** **ANC** + (Low) **Absolute Lymphocyte Count** **ALC** = $\frac{\textbf{High ANC}}{\textbf{Low ALC}}$ = **High Neutrophil Lymphocyte Ratio**



GM-CSF

+



Chemotherapies & CPIs

= ***Win the Battle…***
Lose the War

2025 to 2030: Fighting Dogma

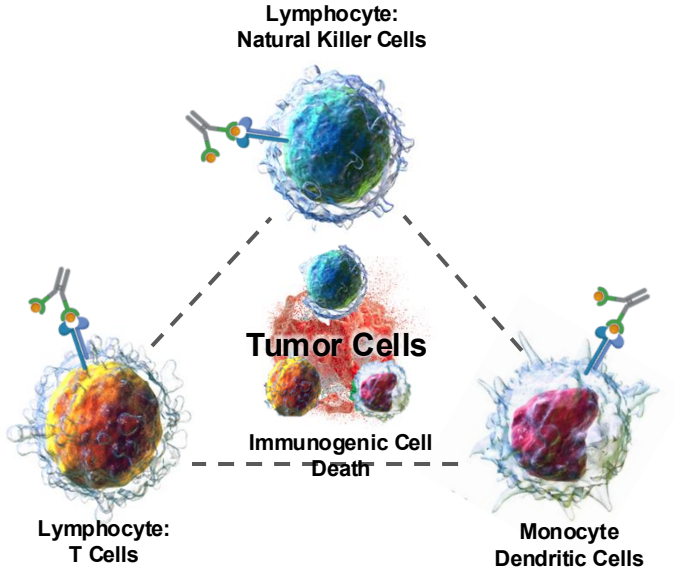
The Power of the Immune System in Urology and All Cancers

Overcoming the Barriers to the Cure

No Immunosuppressive T Regulatory Cells + **Increased Lymphocyte Count** = **T Cell Memory & Durable CR**

The Immune BioShield

+



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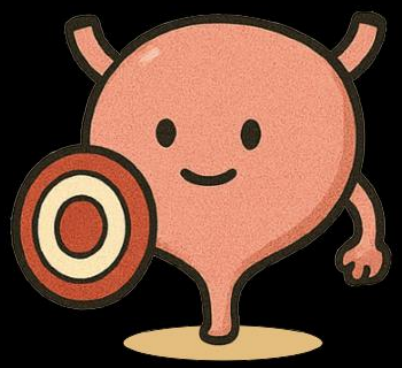
Win the Battle…
Win the War

IL-15 Superagonist ANKTIVA

Activated & Proliferated Lymphocytes

Ongoing CR 9+ Yrs in BCG Naïve NMIBC CIS & Papillary

Immune Protected Bladder: Anktiva + BCG



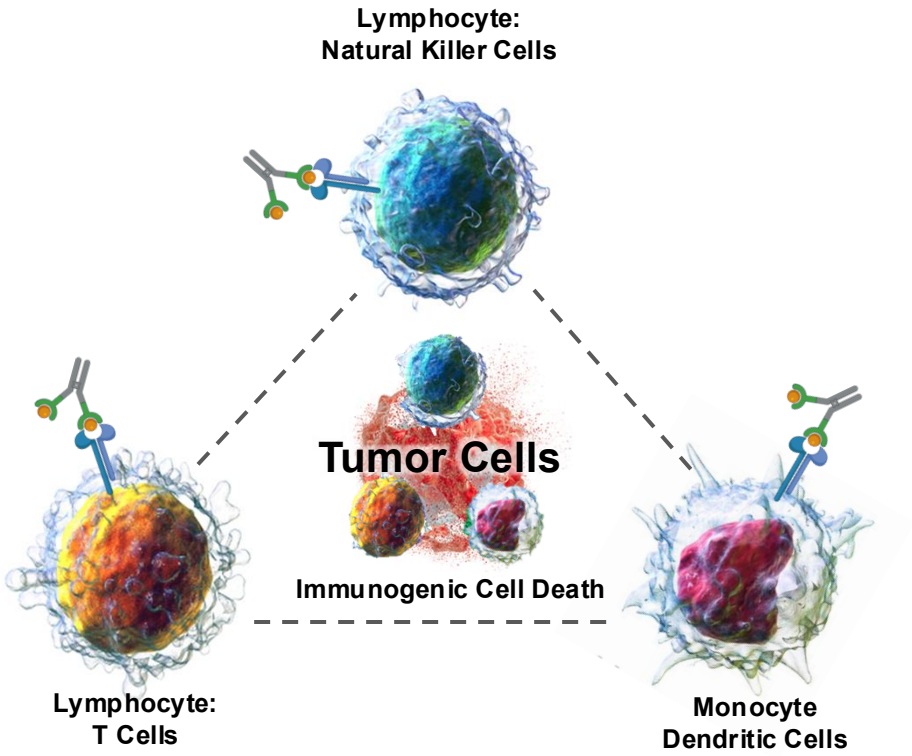
Immune Protected Healthy Bladder

NK, T Cells, and Memory T Cells

Lymphocyte Stimulating Agent

The Missing Link

ANKTIVA



Long-Term Duration of Response with Memory T Cells
53+ Months Duration of Complete Response
>3 Years Cystectomy Avoidance

"Win the battle… Win the war."

2022: Non-Muscle Invasive Bladder Cancer CIS & Papillary Disease

NEJM Evidence

Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

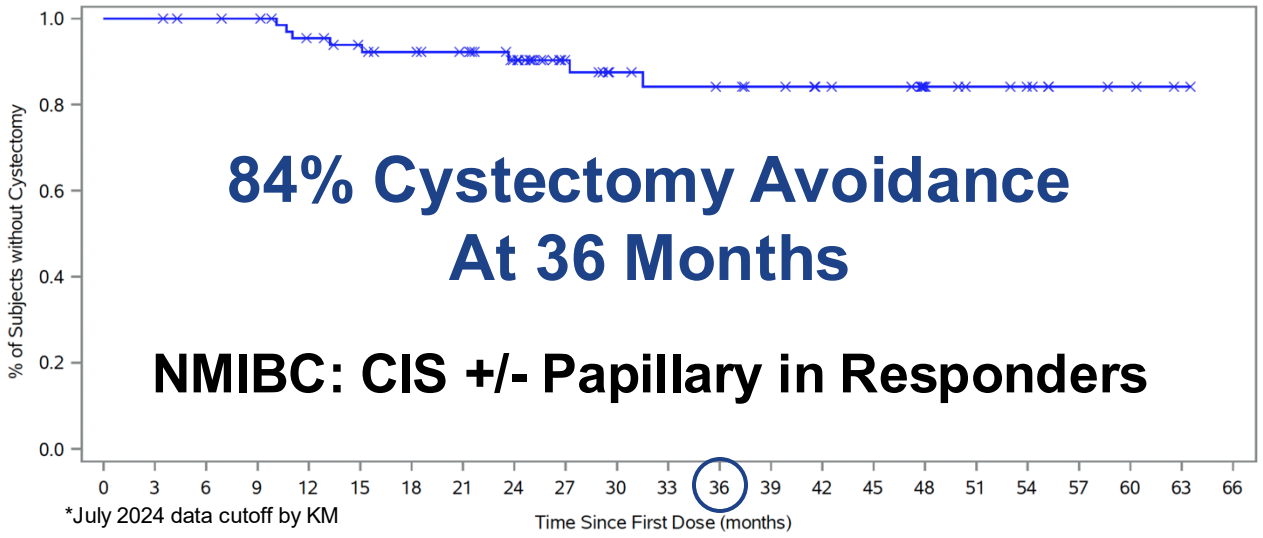
Abstract

BACKGROUND Patients with Bacillus Calmette–Guérin (BCG)–unresponsive non–muscle-invasive bladder cancer (NMIBC) have limited treatment options. The immune cell–activating interleukin-15 (IL-15) superagonist Nogapendekin alfa inbakicept (NAI), also known as N-803, may act synergistically with BCG to elicit durable complete responses (CRs) in this patient population.

2025: NAI + BCG Induces Long-Term Memory and Cystectomy Avoidance Independent of Tumor Type in BCG Unresponsive NMIBC
36 Month Update

FDA Approved 2024

Time to Cystectomy
Efficacy Population – Cohort A (CIS with or without Papillary)



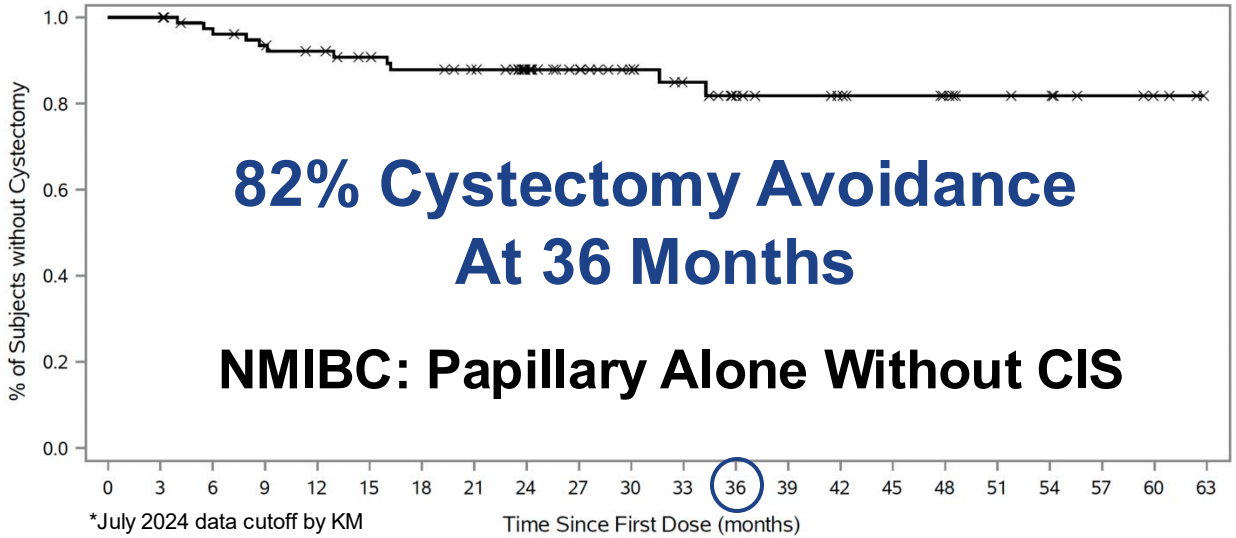
*July 2024 data cutoff by KM

84% Cystectomy Avoidance At 36 Months

NMIBC: CIS +/- Papillary in Responders

Supplemental BLA Filed 2025, Awaiting Approval

Time to Cystectomy
Efficacy Population – Cohort B (Papillary without CIS)



*July 2024 data cutoff by KM

82% Cystectomy Avoidance At 36 Months

NMIBC: Papillary Alone Without CIS

Awaiting NCCN Guidance Approval

Efficacy in **BOTH** CIS +/- Papillary and Papillary alone without CIS demonstrate
Cystectomy Avoidance ≥80% and **Disease Specific Overall Survival ≥96% at 36-months**

2025: NAI + BCG Induces Long-Term Memory and Cystectomy Avoidance Independent of Tumor Type in BCG Unresponsive NMIBC
36 Month Update

NMIBC: CIS +/- Papillary

FDA Approved 2024

BCG Unresponsive NMIBC CIS +/- Papillary	
Cystectomy Avoidance	
Cystectomy-Free Rate at 12 months	**96%**
Cystectomy-Free Rate at 24 months	**90%**
Cystectomy-Free Rate at **36 months**	**84%**
Disease Specific Overall Survival % (N=100)	
12 Months	**100%**
24 Months	**99%**
36 Months	**99%**

*July 2024 data cutoff by KM

NMIBC: Papillary Alone Without CIS

Supplemental BLA Filed 2025, Awaiting Approval

BCG Unresponsive NMIBC Papillary	
Cystectomy Avoidance Rate (N=80)	
Cystectomy Free Rate at 12 Months	**92%**
Cystectomy Free Rate at 24 Months	**88%**
Cystectomy Free Rate at **36 Months**	**82%**
Disease Specific Overall Survival % (N=80)	
12 Months	**99%**
24 Months	**96%**
36 Months	**96%**

*July 2024 data cutoff by KM

Awaiting NCCN Guidance Approval

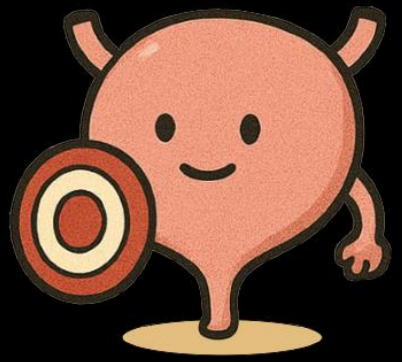
Efficacy in **BOTH** CIS +/- Papillary and Papillary alone without CIS demonstrate **Cystectomy Avoidance ≥80%** and **Disease Specific Overall Survival ≥96% at 36-months**

The Power of the Immune System Overcoming Barriers to the Cure

The Biological Mechanism of Action Determines Long-Term Memory, Duration of Response and Safety

Clinical Impact	IL-15 Superagonist Activating NK & T Cells without Upregulating T Reg Cells	Chemotherapy Inducing Lymphopenia and Suppressive MDSCs and T Reg Cells	GM-CSF Inducing Immuno-Suppressive Myeloid Derived Suppressor Cells (MDSC)	Checkpoint Inhibitor Inducing Lymphopenia and MHC-I Loss
Safety Consistent with BCG	✓	X	✓	X
Durable Complete Response at >48 Months	✓	X	X	X
Cystectomy Avoidance ≥80% at 36-Months	✓	X	X	X
Ease of Administration Consistent with BCG Alone	✓	X	X	X
Logistics of Administration (Timing in clinic) Consistent with BCG Alone	✓	X	X	X
Logistics of Storage of Drugs 2-8 C°	✓	✓	X	✓

The Bladder's Quantum State



Immune Protected Healthy Bladder

NK, T Cells, and Memory T Cells

Immune Compromised Bladder

GM-CSF Suppressor Neutrophils Myeloid Derived Suppressor Cells

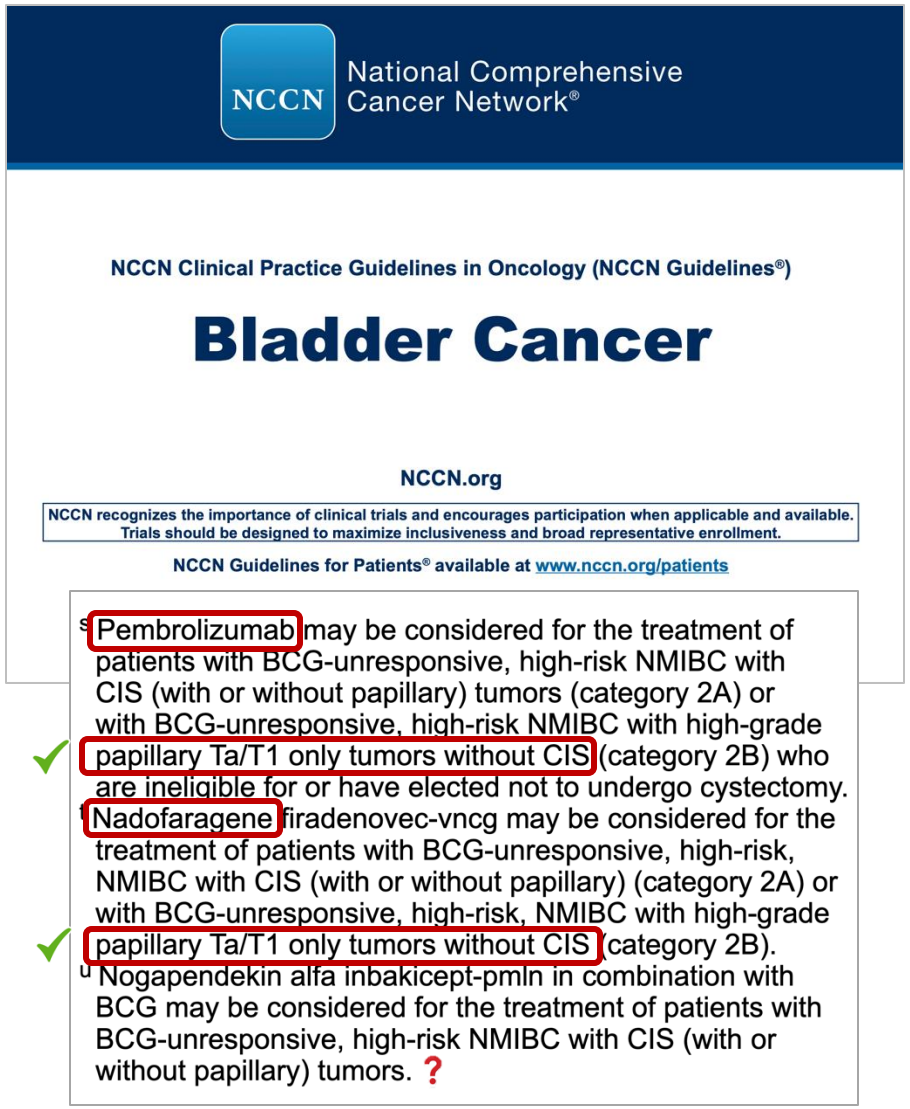
Crippled Painful Bladder

Chemotherapy Lymphopenia

The Lost Bladder

Total Radical Cystectomy

NCCN Inconsistent Policy



National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bladder Cancer

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at www.nccn.org/patients

s Pembrolizumab may be considered for the treatment of patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors (category 2A) or with BCG-unresponsive, high-risk NMIBC with high-grade papillary Ta/T1 only tumors without CIS (category 2B) who are ineligible for or have elected not to undergo cystectomy.

t Nadofaragene firadenovec-vncg may be considered for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with CIS (with or without papillary) (category 2A) or with BCG-unresponsive, high-risk, NMIBC with high-grade papillary Ta/T1 only tumors without CIS (category 2B).

u Nogapendekin alfa inbakicept-pmln in combination with BCG may be considered for the treatment of patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors. ?

NCCN Guidelines Approval for BCG Unresponsive Papillary Disease Only
Nadofaragene, Pembrolizumab vs. Anktiva

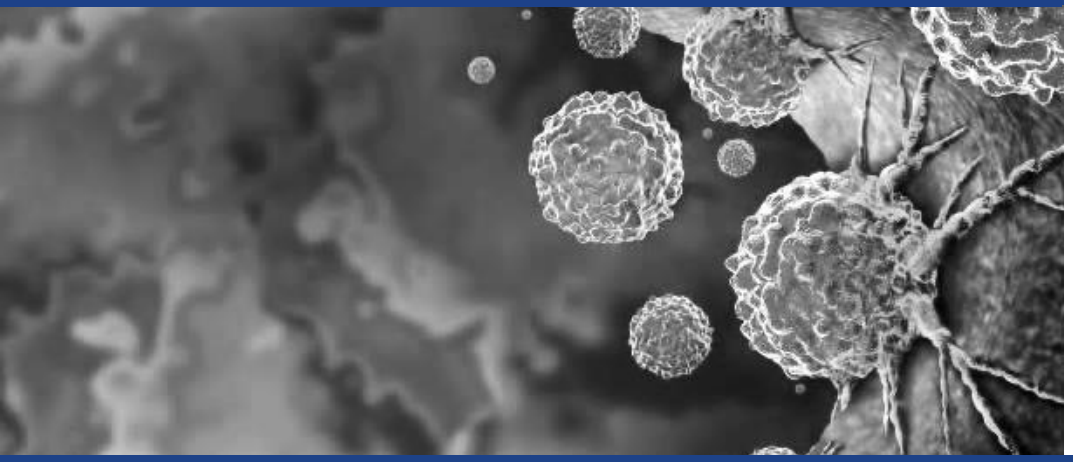
NMIBC Papillary Only Indication	Nadofaragene	Pembrolizumab	Anktiva
Cystectomy Free Rate at 12 Months	86%	76%	92%
Cystectomy Free Rate at 36 Months	No Data	45%	82%
Treatment Related AE's	3.8 Grade 3s	~14% Grade 3s Immune Related AE	3% Grade 3 No Immune Related AE
FDA Approval	No	No	No
BLA Submission	No	Unknown	Supplemental Submitted
NCCN Guidelines: "Papillary only tumors without CIS"	Yes ✓	Yes ✓	No ?
Company	Ferring	Merck	ImmunityBio

Never quit…
Fight dogma…
Ignore naysayers…
Follow the science…
Follow your passion…
Courage of your convictions…
Purposeful impactful innovation…

The only interest to be considered is that of your patients

Patrick Soon-Shiong, MBBCh, MSc, FRCS(C), FACS

Thank You



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