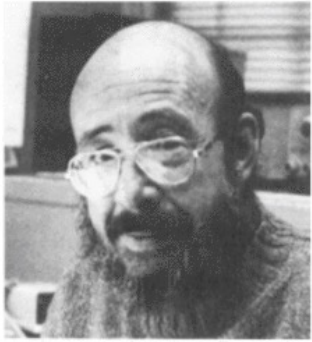
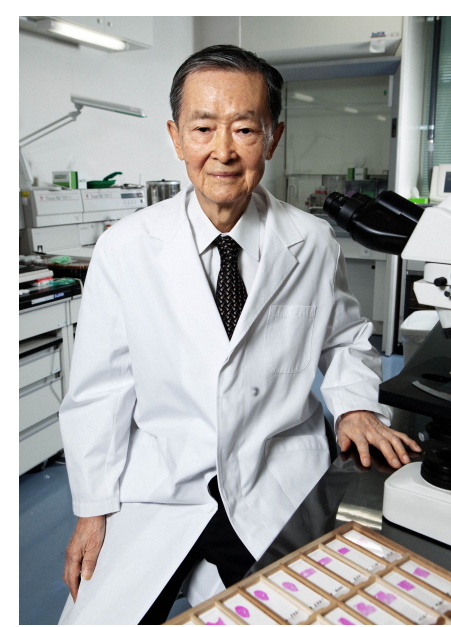


Attenuated Virus Vaccine Technology



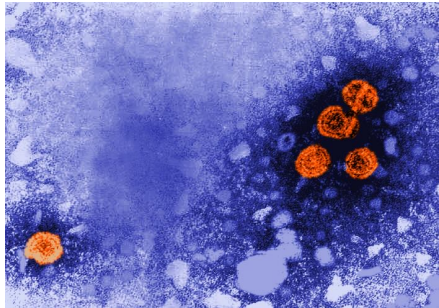
Dr. Alfred M. Prince



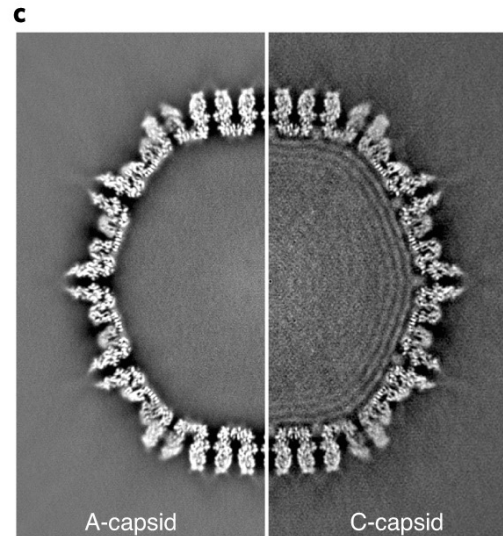
Dr. Michiaki Takahashi

Kirsten Turlo, PhD
Continuing Lecturer
Biomedical Research Minor

UCLA



Dr. Wolf Szmuness



A-capsid

C-capsid



Edward Scolnick, MD

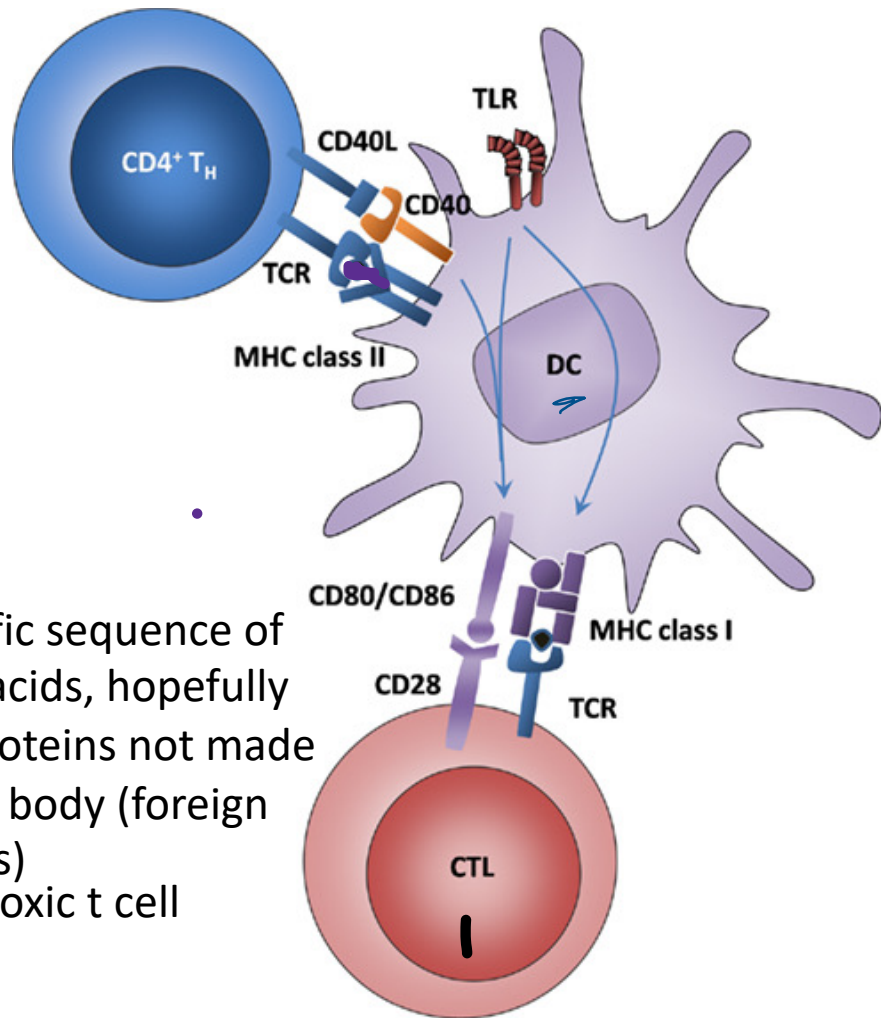
Learning Outcomes

- To understand the role of the scientist in research and the value of research in directing best practices

Learning Objectives

- To be able to describe attenuated virus as a vaccine technology
 - attenuated virus vaccines (varicella/chicken pox - Takahshi 1974),
- To be able to describe the evidence the varicella vaccine is effective at generating an immune response.

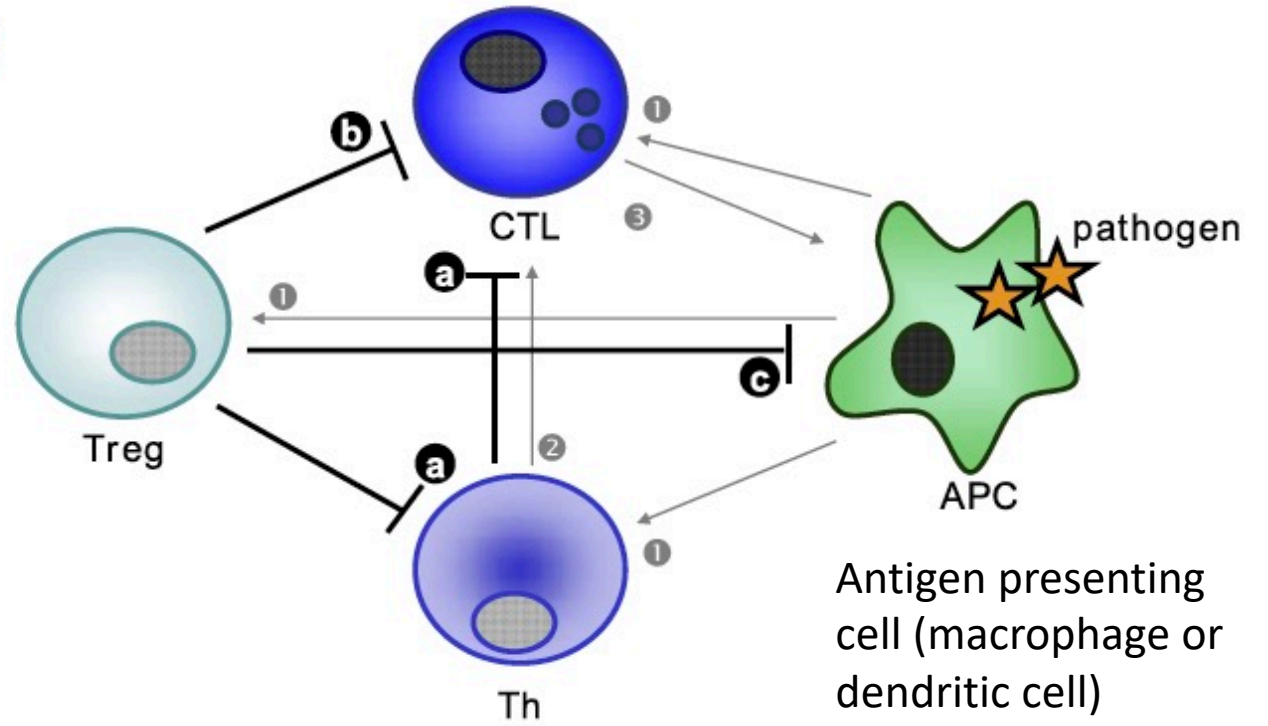
Activation of the Adaptive Immune system



A specific sequence of amino acids, hopefully from proteins not made by your body (foreign proteins)
Cytotoxic t cell

Thaiss, et al (2011) *Frontiers in Immunol*

B



Antigen presenting cell (macrophage or dendritic cell)

pathogen (3). (B) Pathogen specific activation of Tregs may also occur. Tregs can inhibit both proliferation and cytokine production of Th cells, thereby indirectly inhibiting CTL activation (a). Tregs can also inhibit CTLs directly, limiting their cytotoxic capacity (b). An additional option is modulation of the APC by the Treg (c), but the effects of this pathway on pathogen eradication have not yet been studied.

Jooston, et al (2008) *Human Immunol*

DC: dendritic cell. Cells that take up extracellular and cellular materials to activated the immune system (macrophages)

Th: T helper cell (type of t-cell) activates T cells

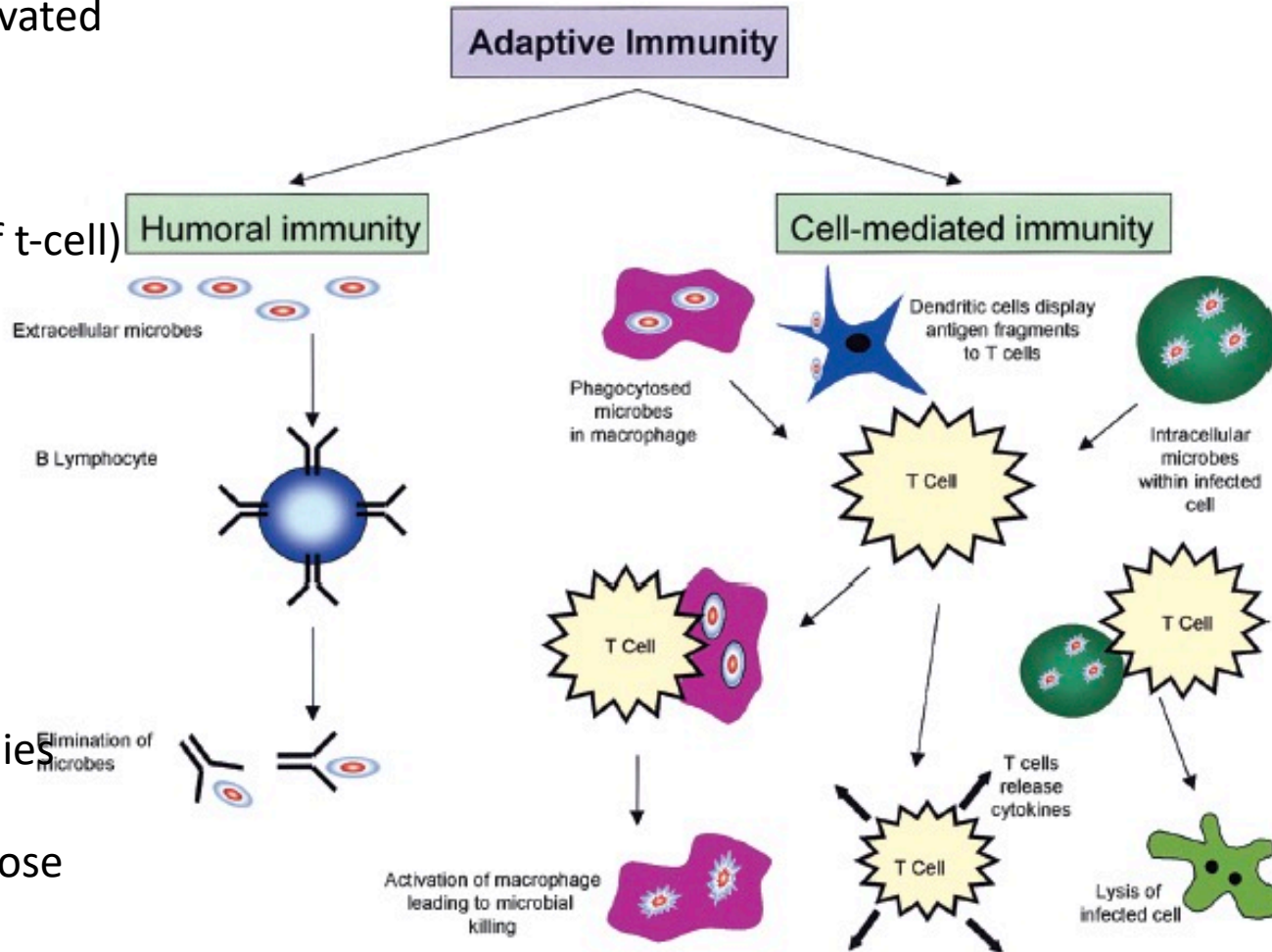
CD3+ cell: T-cell

CD4+ cell: T-helper cells

CD8+cell: killer T-cells

B-cell: produces antibodies

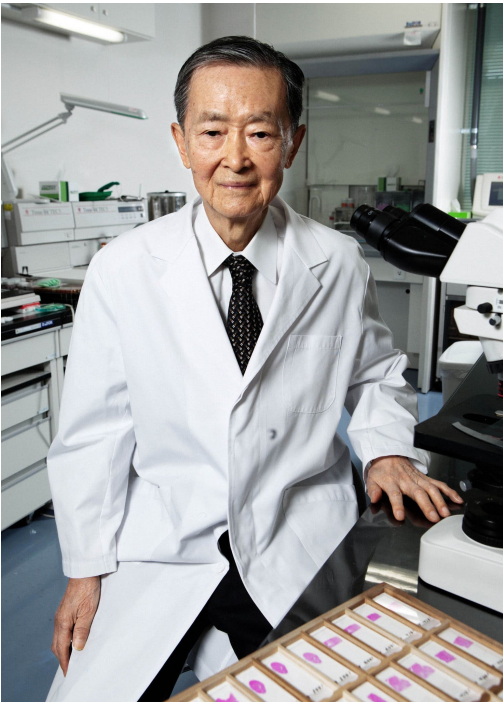
Macrophages: phagocytose (take in or consume) debris/cells/bacteria



Process & breakdown the protein

Takahashi, et al (1974) *The Lancet*

- Question: Can attenuated varicella (chicken pox) virus be used to prime the immune system, without detrimental infection?
- Hypothesis: Weakened varicella virus injection can reduce likelihood of detrimental infection.



Dr. Michiaki Takahashi



Google doodle 2/17/2022

Methods

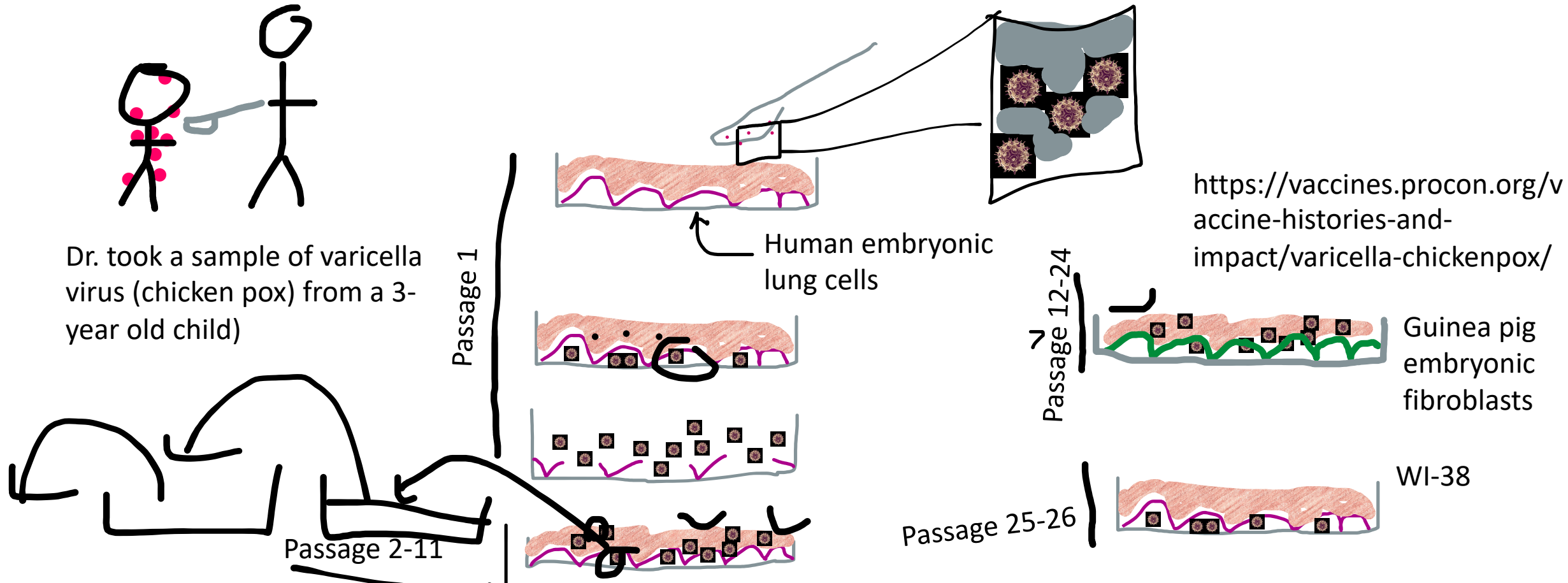
Vaccine Preparation

The virus used was isolated from a three-year-old boy diagnosed as having typical varicella (Oka strain). The virus was serially cultivated eleven times in human embryonic lung (H.E.L.) cells and then in G.P.E. cells. After a twelfth passage in G.P.E. cells, the virus was additionally propagated in human diploid cells (WI-38) cells (Flow Laboratories). G.P.E. cells were obtained by trypsinisation of skin and muscle tissues from three to four-week-old guineapig embryos. Passage of virus was

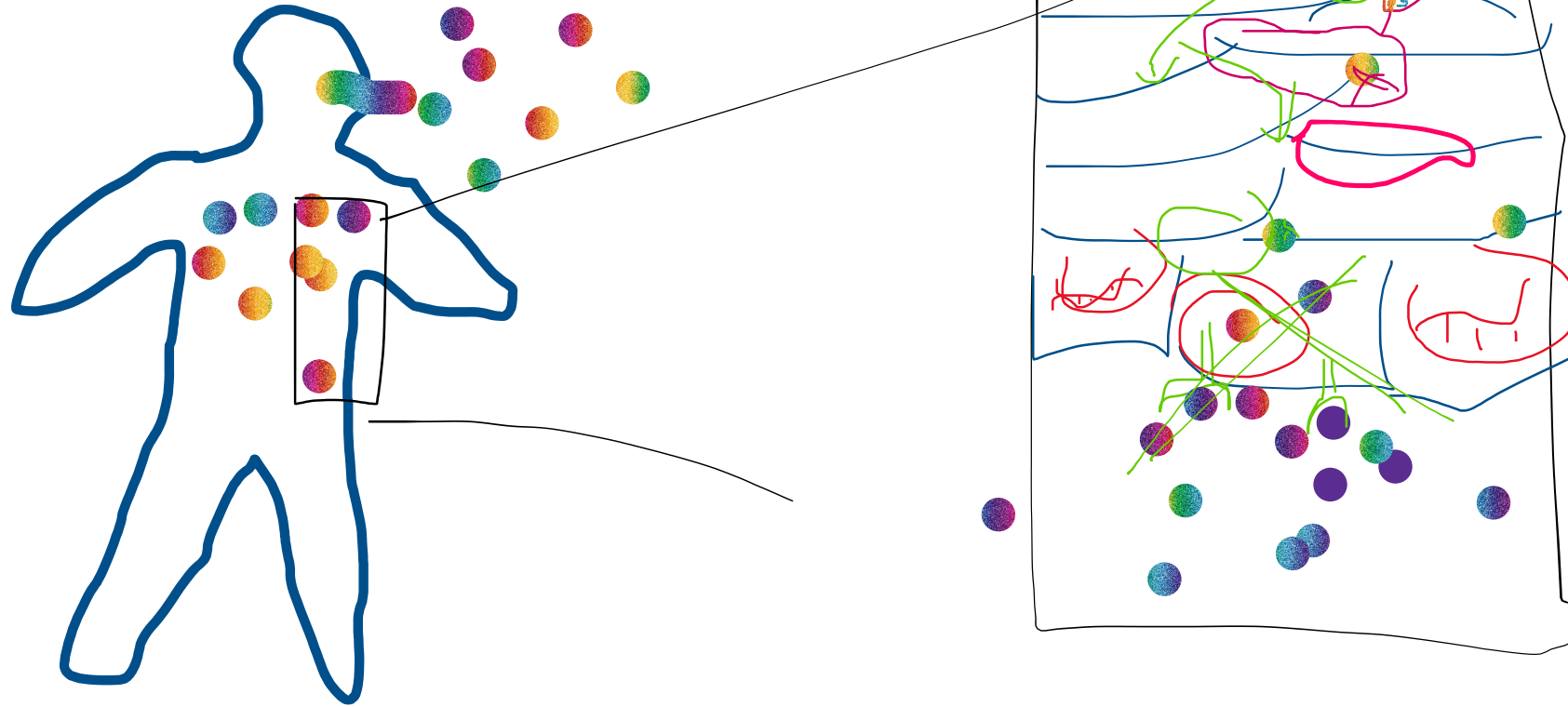
What is an attenuated virus?

Live-attenuated virus: contains a version of the virus that has been weakened in the laboratory.

Adapted from: <https://www.niaid.nih.gov/research/vaccine-types>



How are vaccines made and how do they work?



Results

TABLE I—ANTIBODY RESPONSES IN HEALTHY CHILDREN AT HOME GIVEN VARIOUS DOSES OF VARICELLA VACCINE SUBCUTANEOUSLY

Vaccine dose* (P.F.U.)	Seroconversion	Mean C.F. antibody titre
500*	19/20†	2 ^{3.8}
200*	11/12	2 ^{3.6}
100*	7/9	2 ^{3.6}
200‡	9/9	2 ^{4.0}
1000‡	11/11	2 ^{4.4}
2000‡	10/10	2 ^{4.7}

* Oka strain of varicella virus passaged 11 times in H.E.L. cells and 6 times in G.P.E. cells.

† Number in which seroconversion occurred/number vaccinated.

‡ Oka strain of varicella virus passaged 11 times in H.E.L. cells, 12 times in G.P.E. cells, and twice in WI-38 cells.

Results

and $2^{4.7}$ (table 1). There were no clinical reactions due to vaccination. Thus passage in G.P.E. cells and WI-38 cells attenuated the Oka strain of varicella virus which could then be safely and effectively used to vaccinate susceptible children.

Conclusion?

Learning Objectives

- To be able to describe attenuate virus as a vaccine technology
 - attenuated virus vaccines (varicella/chicken pox - Takahshi 1974),
- To be able to describe the evidence the varicella vaccine is effective at generating an immune response.

Learning Outcomes

- To understand the role of the scientist in research and the value of research in directing best practices

*Vaccination of Children in Hospital Immediately
after a Case of Varicella was Found*

The attenuated virus was then used to vaccinate children in hospital to prevent the spread of varicella infection. In the children's ward of the Chukyo Hospital, typical symptoms of varicella developed in a three-year-old boy with nephrosis. The diagnosis was later confirmed serologically. At that time there were 54 sick children in the ward and 23 of them had no history of varicella and no detectable c.F antibody against varicella. They had nephritis, nephrotic syndrome, purulent meningitis, &c., and 12 of them had been receiving adrenocortical steroid hormone. These 23 seronegative children were inoculated subcutaneously with the vaccine prepared from the virus after a sixth passage in G.P.E. cells (the infectivity titre was $10^{2.75}$ T.C.I.D.₅₀ per 0.1 ml.) immediately after symptoms of varicella were detected in the initial case. Clinical observations were made daily. Blood

TABLE II—CLINICAL AND SEROLOGICAL RESPONSES IN CHILDREN IN HOSPITAL GIVEN A LIVE VARICELLA VACCINE IMMEDIATELY AFTER A CASE OF VARICELLA OCCURRED

Patient	Age (yr.)	Sex	Underlying disease	Steroid therapy	C.F. antibody titres					Fever			Rash
					0 wk.	1 wk.	2 wk.	4 wk.	10 wk.	Onset (day)	Maximum temperature (°C)	Duration (days)	
1	4	F	Purpura	+	<4	..	32	64	16	13	37.7	1	-
2	3	F	Myelitis	+	<4	..	32	32	-
3	6 mo.	M	Hepatitis	+	<4	32	-
4	1	M	Enteritis	-	<4	32	-
5	8	M	Arthritis	+	<4	..	32	32	8	-
6	11	M	Nephritis	-	<4	16	-
7	4	F	Asthma	-	<4	..	16	32	-
8	4	M	Enteritis	-	<4	..	4	32	16	10	37.5	1	-
9	1	M	Hepatitis	+	<4	..	16	128	32	14	37.5	1	+
10	1	M	P.M.*	+	<4	..	16	16	..	14	37.5	1	-
11	1	M	P.M.	+	<4	8	-
12	1	F	Hæmangioma	+	<4	32	-
13	1	F	v.s.D. †	-	<4	..	64	64	32	-
14	1	M	Hepatitis	+	<4	16	-
15	12	M	Nephrosis	+	<4	32	-
16	4	M	Nephrosis	+	<4	<4	16	64	32	-
17	5	F	Nephritis	+	<4	<4	4	32	..	11	37.5	1	-
18	5	F	Nephritis	-	<4	<4	..	32	-
19	1	F	Nephritis	-	<4	..	32	16	..	11	38.2	1.5	+
20	3	F	Nephritis	-	<4	4	32	-
21	1	M	Nephritis	-	<4	16	-
22	1	F	Enteritis	-	<4	32	-
23	3	M	Nephritis	-	<4	<4	..	32	-

P.M. = purulent meningitis. v.s.D. = ventricular septal defect.