Vaccine Adjuvants

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Disclosure

Employed by GSK where I am a vaccine research physician scientist

Industry Representative Member, National Vaccine Advisory Committee

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Vaccine Science: Two Centuries of Continuous Research, Improvements, and Achievements

R. Thom, *'Jenner: Smallpox is Stemmed, from "The History of Medicine,"'* Collection of the University of Michigan Health System, Gift of Pfizer.
Bonanni P, et al. Chapter 1 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

Current Challenges for Vaccines[1]

Challenging populations due to impaired immune system (eg, elderly, children, immunocompromised)	**Need for booster vaccinations**	**Recombinant antigens** generally less immunogenic than live or attenuated organism vaccine[2]	**Pathogens** that require broad and complex immune response	**Need for antigen sparing** potential supply problems (eg, pandemic flu)
Increase the level of the immune response	**Prolong** the duration of the immune response, improve immune memory, and protection	**Overcome** a weakened immunogenicity	**Induce** the generation of a high and broad immune response	**Reduce** the amount of antigen needed (dose-sparing)

1. Garçon N, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011; Chapter 4: 89-113.
2. Petrovsky N, Aguilar JC. *Immunol Cell Biol*. 2004;82:488-496.

Examples of Novel Approaches to Vaccine

DNA[1]	Live vectors[1]	Reverse vaccinology[1]	Self-amplifying RNA[2]	Novel adjuvants and adjuvant combinations[3]
• Pathogen-derived genetic material coding for the antigens contained in a non-replicating DNA plasmid • Antigen is expressed by the cells of the vaccine recipient	• Targeted antigens encoded by gene(s) incorporated into the vector's genetic material • Antigens expressed by a vector (like virus or bacterium) that is non-pathogenic	• Computer analysis of the pathogen's entire genome is conducted to find genes that may be antigenic • Vaccine candidate identified based on prediction of protein sequences similar to pathogen's genome sequences	• Synthetic virus particles include antigen proteins • Once inside host cell cytoplasm, these self-amplify in large amounts, express antigen proteins and interact with the host immune system	• Substances included in a vaccine formulation to enhance the quality and strength of the immune response induced by the vaccine antigen(s)

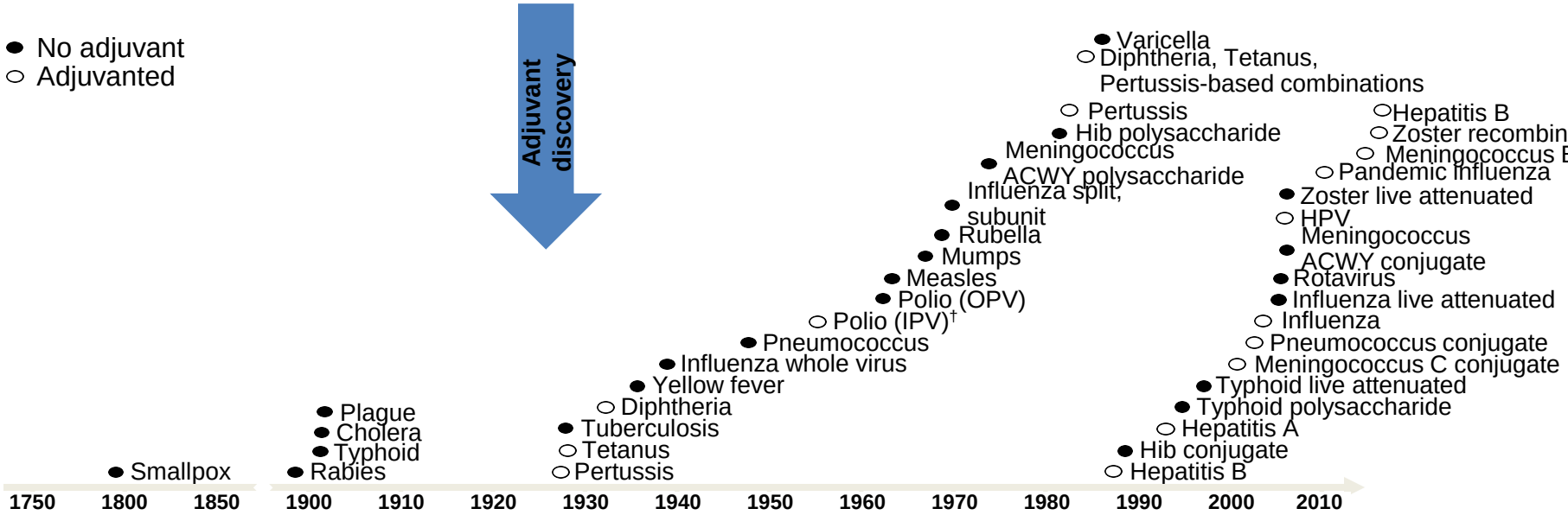
1. Stanberry L, Strugnell R. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011; Chapter 6: 155-199.
2. Geall A, et al. *Semin Immunol*. 2013;25:152-159.
3. Garçon N, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011; Chapter 3: 61-88.

Adjuvant[1,2]

- From Latin, *adiuvare*: to aid
- Substance included in a vaccine to enhance and modulate the quality and/or strength of the immune response induced by the antigen
- Old technology, made new

1. Bonanni P, et al. Chapter 5 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.
2. Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

Vaccines With or Without Adjuvants



†IPV is adjuvanted when formulated in combination with diphtheria, tetanus, pertussis-based vaccines, but is not adjuvanted when formulated as a standalone vaccine.
Hib= Haemophilus influenzae type b; HPV= human papilloma virus; IPV= inactivated polio vaccine; OPV= oral polio vaccine (live).
Adapted from Strugnell R, et al. Chapter 3 and Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

Antigens May Need Help: The Role of Adjuvants

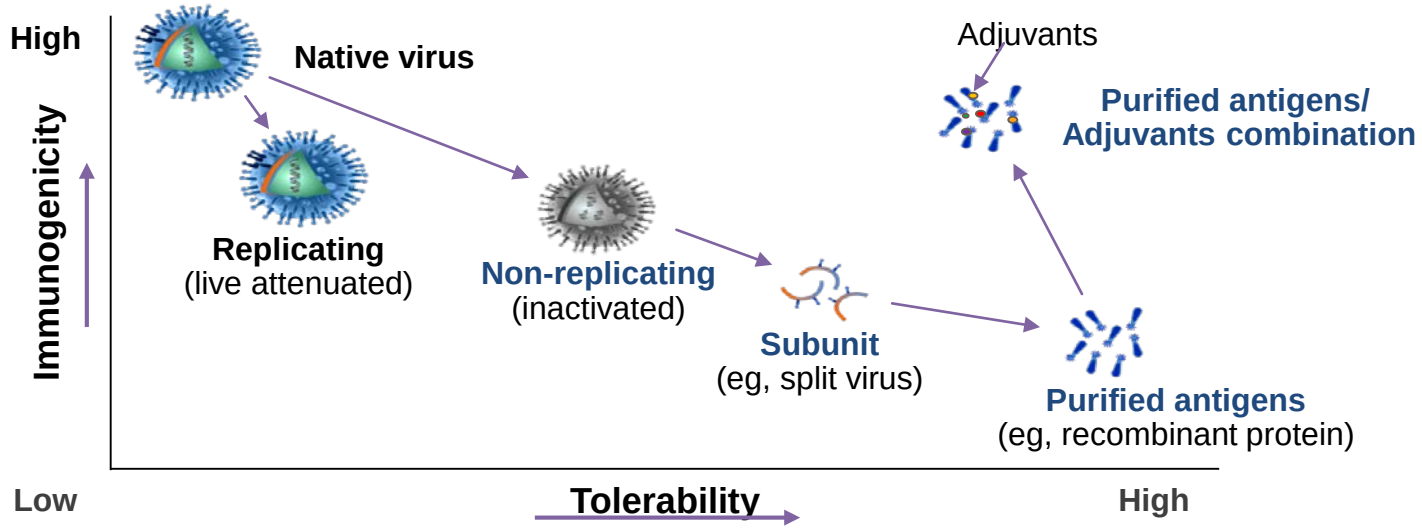


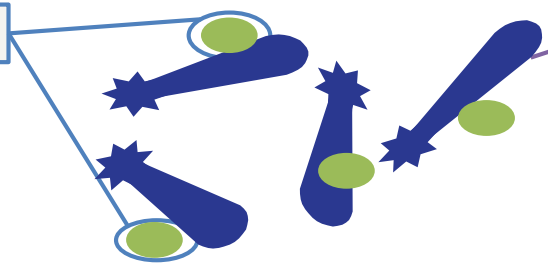
Figure adapted from Di Pasquale A, et al. *Vaccines*. 2015;3:320-343.

Adjuvants Work by Stimulating Innate Immunity

Innate immune system
Required for the onset

Adjuvant[1]

- Recognized by specific receptors (TLRs, NLRs)
- Stimulate antigen presentation to cells from adaptive immunity (specific T- and B-cells)



Adjuvanted vaccine

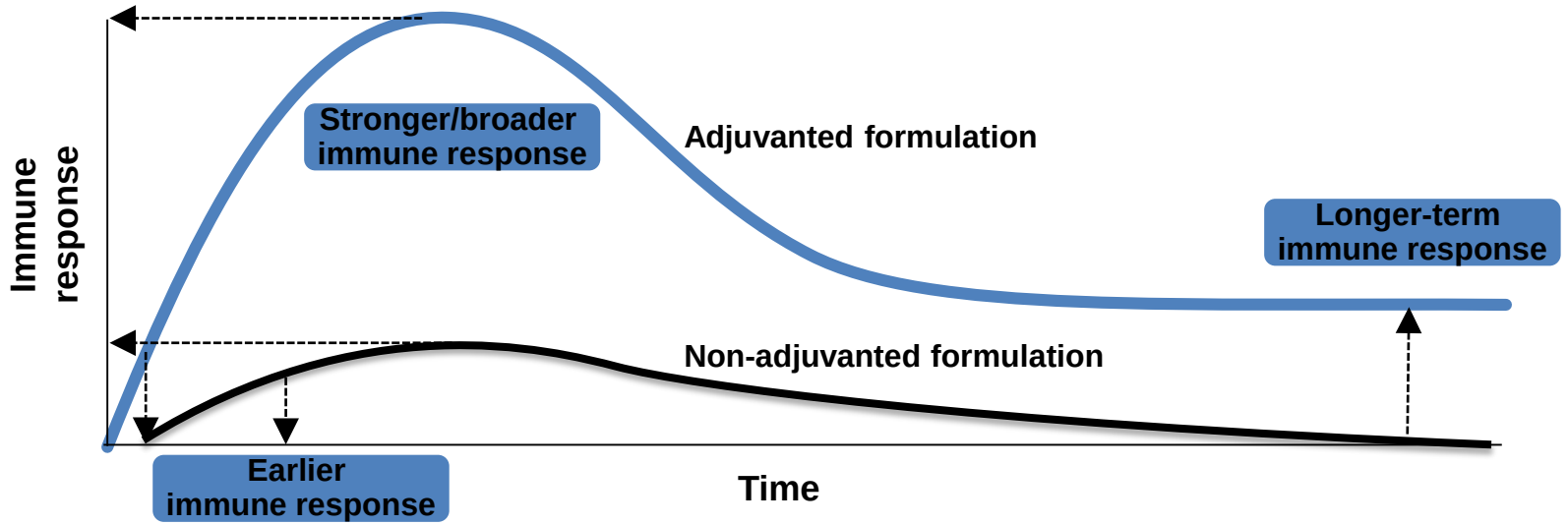
Adaptive immune system
Specific, provide memory

Antigens[2]

- Antigen-specific T- and B-cells provide the specificity to the vaccine
- Memory T- and B-cells confer long-term protection against disease

1. Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.
2. Leo O, et al. Chapter 2 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

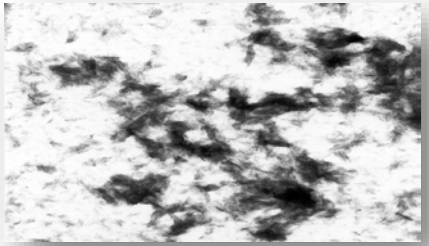
Expected Impact of Adjuvants on Vaccine Immune Response



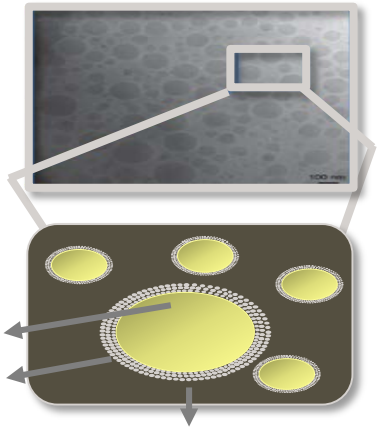
Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

Different Categories of Adjuvants Have Been Developed

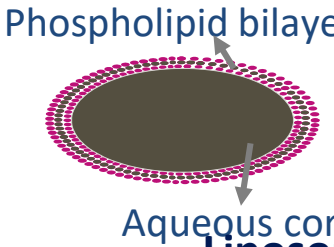
Mineral salts



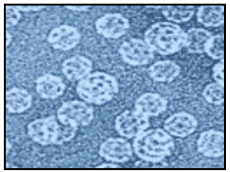
Emulsions



Particulate Formulations



Liposomes



Saponin complexes

Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

Adjuvants–Few Approved, Many in Development

Adjuvants in Licensed Products

Adjuvant	Mechanism or Receptor	Licensed product
Aluminum salts	Nalp3, ITAM, antigen delivery	Numerous (eg, pertussis, hepatitis, pneumococcal)
AS04	TLR4	HPV
Emulsions (MF59, AS03)	Immune cell recruitment, antigen uptake	Influenza
AS01	TLR4, inflammasome	Zoster
CpG ODN	TLR9	Hepatitis B

Adjuvants in Development

Adjuvant	Mechanism or receptor	Clinical phase
ISCOMs (Matrix-M)	Unknown	2
dsRNA analogues	TLR3	1
Flagellin	TLR5	1
C-type lectin ligands	Mincle, Nalp3	1
CD1d ligands	CD1d	1
GLA-SE	TLR4	1
IC31	TLR9	1
CAF01	Mincle, antigen delivery	1

Adapted from Reed SG, et al. *Nature Med*. 2014;19:1597-1608.

Observed Benefits of Adjuvants in Candidate or Licensed Adjuvanted Vaccines

- Efficacy demonstrated for different antigens: split (influenza)[1], parasite-derived (malaria)[2], viral glycoprotein (herpes zoster)[3], viral particles (HPV)[4]
- Persistent increase in T-cell and antibody response in magnitude and quality (antibody breadth and cross-reactive T-cells)[1,5]
- Benefits shown across the entire age spectrum (6-month-old infants to >80-year-old-adults)[3,6] with the possibility to adapt dosage to age (eg, use of lower dose in pediatric formulation)[6]
- Being used in vaccines in special populations, such as in immunocompromised or HIV+, with acceptable safety outcomes[7]

1. Leroux-Roels I, et al. *PLoS One.* 2008;3:e1665. *2.* RTS, S Clinical Trials Partnership. *N Engl J Med*. 2011;365:1863-1875. 3. Lal H, et al. *N Engl J Med.* 2015;372:2087-2096. 4. Roteli-Martins, et al. *Hum Vaccin Immunother.* 2012;8:390-397. 5. Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011. 6. Knuf M, et al. *Hum Vaccin Immunother*. 2015;11(2):358-76. 7. Denny L, et al. *Vaccine*. 2013;31:5745-5753.

Safety Is of Primary Importance From the Start of Development and Throughout the Entire Life of a Vaccine

- Vaccines are carefully evaluated under tight process controls and overseen by regulatory authorities
- Safety monitoring designed to rapidly identify rare and/or serious adverse events temporally linked to vaccination

Leroux-Roels G, et al. Chapter 5 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

General Reactogenicity and Safety

- Adjuvanted vaccines often have increased reactogenicity, especially at the injection site
- Local symptoms are usually mild/moderate, short-lasting and do not impact compliance

The safety profile of aluminum salt adjuvants has been well established through the use of billions of doses, in different populations, over more than 80 years

Licensed, adjuvanted vaccines have clinically acceptable benefit-risk ratios

Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

One Size Does Not Fit All

No universal adjuvant to cover all vaccine needs

Different diseases may require different immune responses to elicit protection through vaccination

Appropriate selection of adjuvant-antigen combination is key to the formulation of novel and efficacious vaccines

Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

Among All the Possibilities, How Is An Adjuvant Selected?[1,2]

Understand:

- Host-pathogen interaction
- Antigen selection and production
- Optimized immunological tools

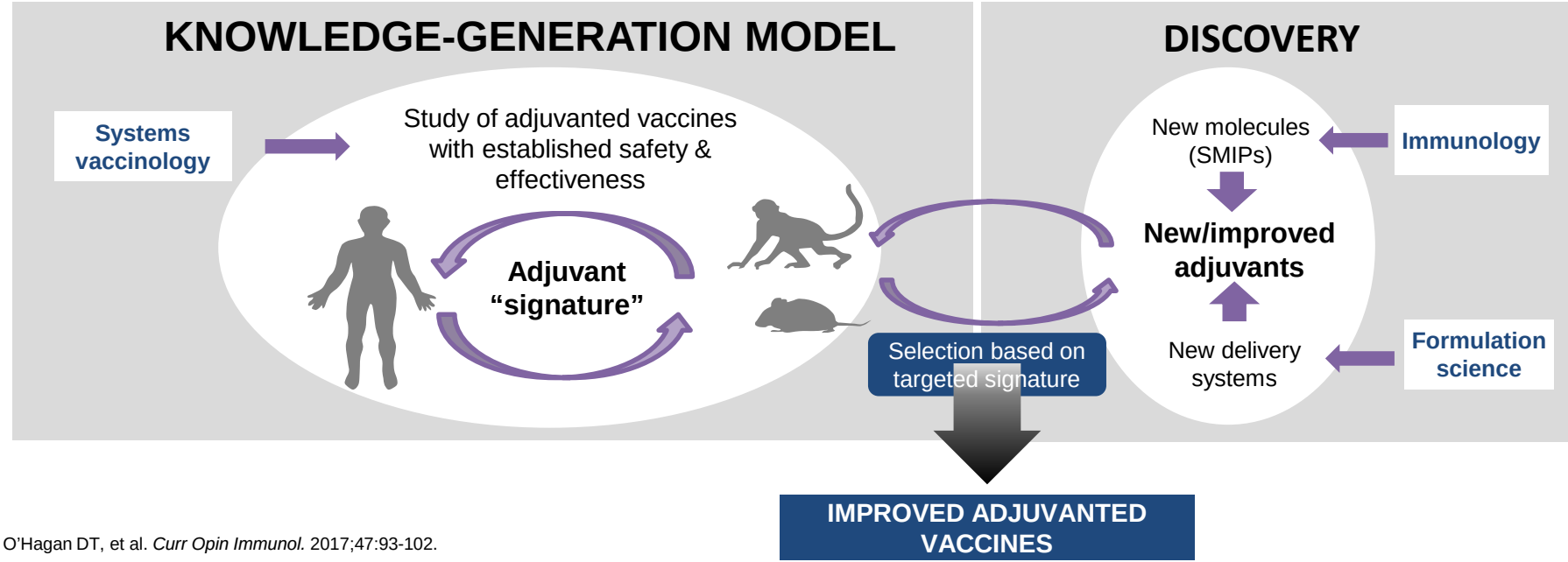
→ Identify need for adjuvant

In case classical aluminum not sufficient, consider: →

- Compatibility with antigen?
- Stability over time?
- Immune response?
- Safety and reactogenicity?

1. Reed SG et al. *Nature Med*. 2014;19:1597-1608.
2. Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

Tools to Develop the Next Generation of Adjuvants



O'Hagan DT, et al. *Curr Opin Immunol.* 2017;47:93-102.

Considerations for NVAC

- More efforts are needed to highlight the importance of novel adjuvants in ongoing vaccine research and their potential to prevent many more infectious diseases through vaccination. As industry, we often say, "the low hanging fruit has been picked." Remaining vaccine targets are exceptionally difficult.
- Advances in understanding how adjuvanted vaccines interact with the immune system should help in mitigating health risks and in better analyzing those events when they occur. Considering the increasing importance of vaccine confidence, public perceptions of adjuvants should be assessed.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