Immunisation
instilling good memories

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WARNING: IMMUNOLOGIST

In case of emergency:
please use acronyms!
• Goal of immunisation
• Memory – what is it?
• Memory – how do we get it?
• Memory – how long does it last?
• Is all memory the same?
• What else can we do with memory?
Summary (immunologose)

- IL-6
- TGF-β
- IFN-γ
- TNF-α
- IL-12
- CD4
- CD28
- memory
- antigen
- antibody
- co-stimulation

vaccine → immunity
natural immunity

memory with disease
immunisation

memory without disease
Building on natural immunity
Building on natural immunity

[Image of a person + virus to result in a person with immunity]
Building on natural immunity
Building on natural immunity
What is memory?

immune cell

army of immune cells

memory

What is memory?
Inducing a response

- live attenuated
- inactivated (killed)
- 2-3 purified antigens
- 1 purified antigen
Inducing a response

1. live attenuated
2. inactivated (dead)
3. 2-3 purified antigens
4. 1 purified antigen
Inducing a response

- live
- attenuated

- inactivated
- (dead)

- 2-3 purified antigens

- 1 purified antigen

Persistence

Inducing a response

- Live attenuated
- Inactivated (dead)
- 2-3 purified antigens
- 1 purified antigen

Adjuvant
Inducing a response

1. Purified antigen
2-3 purified antigens
1 purified antigen

- Live attenuated
- Inactivated (dead)

aluminium salts
What cells?

- Lymphocytes
- Killer T cell
- Helper T cell
- B cell

Inside cell vs. outside of cell
Where does memory fit in?

immune cell

army of immune cells (activated)

die

memory cells (resting)
Why is memory so good?

- immune cell
- army of immune cells
- helper T cells
- killer T cells
- B cells
- memory cells

- ↑ Frequency
- ↑ Function
- ↑ Affinity
Table II. Foreign pMHC-specific naive T cell frequencies determined by tetramer-based cell enrichment

<table>
<thead>
<tr>
<th>Source</th>
<th>Epitope</th>
<th>Frequency per Million Naive CD4+ or CD8+ T Cells*</th>
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</thead>
<tbody>
<tr>
<td>MHCI HCV</td>
<td>NS3-1073:A2</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>NS3-1406:A2</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Core-132:A2</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>NS5B-2594:A2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Gag-77:A2</td>
<td>6</td>
</tr>
<tr>
<td>HIV</td>
<td>PP65-495:A2</td>
<td>4</td>
</tr>
<tr>
<td>CMV</td>
<td>PA-713:DR1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>PA-401:DR1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>PA-505:DR1</td>
<td>0.2</td>
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</tbody>
</table>


What number of T cells do we have at the start?
What number of T cells do we have at the end?

What number of T cells do we have at the end?

Specific T cells in lungs

How does this affect antibody?

specific antibody titres in serum

naïve lymphocyte

memory lymphocyte

function

ACTIVATED

ACTIVATED
The antibody type controls the function.

- **IgM**: BIG blood complement
- **IgG**: small tissue neutralise

**Diagram:**
- Antibody concentration in serum
- Time intervals:
  - Primary antigen exposure
  - Secondary antigen exposure
  - 10 days
  - 20 days

**Primary Response**
- IgM peak
- IgG peak

**Secondary Response**
- IgM peak
- IgG peak boost
Over time antibodies get better and better.
Over time antibodies get better and better.
Why is memory so good?

- Increase frequency
- Easy to activate
- Programmed response
- Long-lived
We found that more than 90% of volunteers vaccinated 25–75 years ago still maintain substantial humoral or cellular immunity (or both) against vaccinia, the virus used to vaccinate against smallpox. Antiviral antibody responses remained stable between 1–75 years after vaccination, whereas antiviral T-cell responses declined slowly, with a half-life of 8–15 years. If these levels of immunity are considered to be at least partially protective, then the morbidity and mortality associated with an intentional smallpox outbreak would be substantially reduced because of pre-existing immunity in a large number of previously vaccinated individuals.

How long is long-lived?

Most T cells formed in first few years of life

\[ \text{% VV-specific memory B cells per total IgG+ memory B cells} \]

\[ 0 \quad 10 \]

\[ 0 \quad 0.001 \quad 0.01 \quad 0.1 \quad 1 \]

\[ 0 \quad 10 \quad 20 \quad 30 \quad 40 \quad 50 \quad 60 \]

years post-vaccination

Where are memory cells?

- **Central memory**
  - Slower acting
  - Less powerful
  - Reside in lymphoid organs

- **Effector memory**
  - Faster acting
  - More powerful
  - Reside in tissue
Which is better?

Effector memory killer T cells are better at killing than central memory killer T cells

Is all memory the same?

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>protective mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polio</td>
<td>antibody</td>
</tr>
<tr>
<td>Mumps</td>
<td>antibody</td>
</tr>
<tr>
<td>Rubella</td>
<td>antibody</td>
</tr>
<tr>
<td>Influenza</td>
<td>antibody</td>
</tr>
<tr>
<td>HepB</td>
<td>antibody</td>
</tr>
<tr>
<td>Measles</td>
<td>antibody, killer T cells</td>
</tr>
<tr>
<td>Small pox</td>
<td>antibody, killer T cells</td>
</tr>
</tbody>
</table>

**considerations:**

- Location (effector vs central memory)
  - Type of antibody
  - Level of antibody
Is all memory the same?

example: Influenza A

IgG or IgA injected i.v.
Infected with virus intranasally.

1. Viral shedding?
2. Tissue damage?

<table>
<thead>
<tr>
<th>type</th>
<th>nasal virus</th>
<th>pathology</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>nasal</td>
<td>tracheal</td>
</tr>
<tr>
<td>IgA</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>IgG</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

What is the strength of memory?

SPECIFICITY
What is the drawback of memory?

SPECIFICITY
What is the drawback of memory?

SPECIFICITY

IN antibodies

OUT

T cells
How do we instill good memory?  
(optimizing the use of vaccines)

**Vaccine design**
- Each disease has a different **correlate of protection**
- Antibody versus killer T cells
- IgG versus IgA
- Tissue location for effector memory cells
- Central need for helper T cells
- Vaccines must contain **targets** and **signals** for the best response

**Vaccine delivery:**
- Compliance
- Boosters

**Considerations:**
- Age-associated immune decline (Tetanus, influenza, shingles)
- Concomitant medications
- Pre-existing memory
New avenues for use of vaccines

T CELL TARGETED: tuberculosis

THERAPEUTIC: cancer

ANTI-PATHOLOGY: prevent disease not infection

PERSONALIZATION: tailoring to individual

Which memory do you prefer?