Switched memory B cells maintain specific memory independently of serum antibodies
**ADAPTIVE IMMUNE RESPONSE**

**Day 3**
- extra-follicular phase

**Day 7**
- germinal center reaction

**Day 14**
- MEMORY B
- SHORT-LIVED PC
- LONG-LIVED PC
- the products
Resting B cells express antibodies with germline sequence, as antigen-receptors on their surface. They can be induced to secrete antibodies of IgM isotype. Most IgM is pentameric.

Switched memory B cells have been selected for their high affinity to a defined antigen. The receptor is expressed on the cell surface and can be secreted.

Plasma cells have no receptor and cannot sense antigen. They are factories that produce selected, high-affinity antibodies.
THE IDEAL IMMUNE RESPONSE
IS THE CONCENTRATION OF SERUM ANTIBODIES CORRELATED TO THE FREQUENCY OF MEMORY B CELLS?

HEPATITIS B:

COMPARISON BETWEEN TWO VACCINES THAT INDUCE DIFFERENT LEVELS OF ANTIBODIES

Infanrix-Hexa VAC A: 710 pts  34 pts

Hexavac VAC B (831 pts) 65 pts

VACCINEES:  LARGE GROUP 710 Infanrix, 831 Hexavac
            SMALL GROUP   34 Infanrix, 65 Hexavac
We measured
- serum levels of specific antibodies
- and frequency of specific memory B cells
5 YEARS AFTER PRIMARY VACCINATION

HEXAVAC 831 pts
INFANRIX 709 pts

HEXAVAC 63 pts
INFANRIX 35 pts
AFTER BOOST

Frequency of responding patients

VAC A
VAC B

LARGE
SMALL
SERUM ANTIBODIES AGAINST HBsAG ARE LOWER IN THE HEXAVAC GROUP: VANING IMMUNITY?
BOTH GROUPS OF CHILDREN RESPOND EQUALLY WELL TO A BOOSTER DOSE OF HBV VACCINE

![Graph showing the response of boosted children grouped according to serum anti-HBsAg titer.](image)
WHAT ABOUT MEMORY B CELLS?

A

B cells (% of total lymphocytes)

Vac A    Vac B

B

Memory B cells (% of total B cells)

Vac A    Vac B
TLR9: A TOOL TO EXPLORE B CELL MEMORY
Maintenance of serological memory

exclusively through specific recall

restriction of the repertoire

RISK FOR THE INDIVIDUAL AND THE SPECIES
Maintenance of serological memory

through specific and aspecific recall

preservation of a diverse repertoire

EQUILIBRIUM OF THE INDIVIDUAL AND THE SPECIES WITH PATHOGENS
MATURE AND MEMORY B CELLS STIMULATED THROUGH TLR9

1) Survival/proliferation

2) CD27bright cells in CpG stimulated cells

CD27

Untreated

CpG

R1

R2

CD27

Switc

IgM

me

me

memory

mature

CMFDA

IgM

R1

R2

ma

ma

cell subsets
CpG INDUCES THE FORMATION OF FUNCTIONAL PLASMA CELLS FROM MEMORY B CELLS
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>total IgG</th>
<th>HBsAg-IgG</th>
<th>T.Tox-IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine A</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Vaccine B</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>
5 years after vaccination

THE MEMORY POOL OF VAC A AND VAC B GROUPS IS EQUALLY EFFICIENT IN GENERATING PLASMA CELLS UPON CpG STIMULATION
THE FREQUENCY OF ANTI-HBsAg MEMORY B CELLS IS NOT DIFFERENT IN VAC A AND VAC B GROUPS
5 years after vaccination

THE FREQUENCY OF ANTI-HBsAg MEMORY B CELLS IS NOT CORRELATED TO THE CONCENTRATION OF SERUM ANTIBODIES
AFTER BOOST

VAC A AND VAC B GROUPS RESPOND EQUALLY WELL TO BOOST

![Graph showing anti-HBcAg IgG serum concentration pre and post boost for Vac A and Vac B groups.](image-url)
AFTER BOOST

THE FREQUENCY OF ANTI-HBsAg MEMORY B CELLS SIGNIFICANTLY INCREASES AFTER BOOST

p < 0.02
SPECIFIC MEMORY B CELLS ARE FUNCTIONAL IN CHILDREN WITH LOW LEVELS OF SPECIFIC SERUM ANTIBODIES
CONCLUSIONS:

1. Switched memory B cells maintain specific memory independently of serum antibodies

2. Memory B cells and long-lived plasma cells are independently generated

3. The ability to generate short-lived plasma cells differs among individuals
Are memory B cells really able to prevent and control HBV infection?

WHAT HAPPENS IF WE KILL ALL MEMORY B CELLS?
Rituximab is an anti-CD20 monoclonal antibody widely used to eliminate B cells in B-cell lymphoma and autoimmunity.

CD20 starts to be expressed by pre-B cells in the bone marrow; it is high in mature and memory B cells and completely absent in plasma cells.
After more than 10 years of use, rituximab has proven to be remarkably safe. Immunoglobulins levels remain unaltered in most patients, but an increased number of infections has been documented especially in long-term treatments.

The most important infection is hepatitis B reactivation, which may be delayed and result in fulminant liver failure and death. Special care should be placed on screening for hepatitis B and administering preemptive antiviral treatment.
In collaboration with

ALBERTO TOZZI
ALESSANDRO ZANETTI

THANK YOU

THE BEE CELL
GROUP