A chemical mimic of Interleukin 7; why should older people care?

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Top 5 causes of death in the Elderly

- Heart disease (49%)
- Malignant neoplasm (29%)
- Pneumonia & Influenza (6%)
- Cerebrovascular disease (10%)
- Chronic Obstructive Pulmonary disease (6%)

19% of people with ami recall an upper respiratory infection in the 2 weeks before their event.
I want to consider an average individual (John) alive today working on the 3rd floor of a building in London.

John travels to work using the tube and then takes the elevator to his floor.

In an average journey to work approximately 30 individuals will enter John’s zone.

With ten journeys per week this makes 300 possible interactions or 13,800 per year. (He has 6 weeks holiday)

And this is infection by the airborne route only.

Transmission of infection is possible through touching handrails, buttons or other surfaces.

The chance of John becoming infected depends on the state of his immune system.
From an early age we are introduced to antigens, some naturally, some deliberately by vaccination to provoke an immune response.

Successful responses provide our immune system with memory cells capable of recognising and responding more rapidly to potential pathogens presenting the same antigen at a later date.

Theoretically then old individuals must be able to cope with any potential pathogen they have ever met.
Are there any clinical signs suggesting that the immune system is declining with age.
## Epidemiological Evidence
Deaths from Pneumonia and Influenza (ICD-9 Code 480-487) in England and Wales 2000

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<th>15-44yr</th>
<th>45-64yr</th>
<th>&gt;65yr</th>
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<td>53833</td>
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<tr>
<td>%</td>
<td>0.2</td>
<td>0.8</td>
<td>4.3</td>
<td>94.7</td>
<td>100</td>
</tr>
</tbody>
</table>
Clinical data

Protective response to influenza

• Efficacy of influenza vaccine is between 70 and 90% in young adults especially when the vaccine strain resembles the epidemic strain

• Clinical effectiveness of the vaccine declines in the elderly to 30-40% (C. Hannoun, F. Megas, J. Piercy, *Virus Res.* **103**, 133 (2004).)
Laboratory Tests

Senescent T cells (KLRG-1) increase with age.

Human PBL

Mouse PBL

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Voehringer et al J.Imm 2001 167 4838-43
Why are we more susceptible to disease as we grow older?

The immune system seems to wind down with age.
A typical response:

- Antigen presented by APC to a CD4 T cell: Activation → Help
- Antigen presented by APC to a CD8 T cell: Activation → Kill Virus-infected cells
- Antigen presented by APC to a B cell: Help

Secondary lymphoid follicle

[Image of cellular interactions]
Is it the T cells?

The Thymus
Human (20-30yr)
50±10% of blood T lymphocytes
Thymic output declines with age
Thymus/T cell pool changes

Large clones
Most Humans >40
58% of mice >2yr

No decrease in size of T cell pool with age
Senescent T cells, unable to divide further.

Exert regulatory role in vivo
High levels correlate to poor responses to influenza

Consequences of proliferation to maintain numbers

(i) Smaller burst size and limited proliferation

Anti-CD3 proliferation

A = 34 yrs old
B = 86 yrs old

Counts per minute

Days
Current hypothesis about age and immunity

• As we age thymic output falls driving memory cell division
• Memory cells are not immortal so they reach their replication limit.
• Terminally differentiated T cells accumulate with age.
• Some of these may be defective due to replication errors.
• Persistent viral infections eg CMV may lead to further problems by enhancing the process.
Can we reverse age related thymic atrophy?

Methods to rejuvenate the thymus

- castration,
- keratinocyte growth factor
- IL-7
- Ghrelin
IL-7 therapy

3 weeks

Thymic output

Absolute numbers

Saline treated group

IL-7 treated group

proliferation to anti-CD3

counts per minute

Saline treated group

IL-7 treated group

0 2000 4000 6000

0 20000 40000 60000 80000 100000

0 20000 40000 60000 80000 100000

O +S O +iL-7

y O +S O +iL-7

δEC
Vaccination with A/PR/8/34 influenza virus

The study comprised 6 female Rhesus macaques (*Macaca mulatta*) whose average age was 20 years old (range 18.5 to 23.9) at the start.

Recombinant simian IL-7 s/c 60µg/kg alternate days for 14 days OR saline vehicle alone.
Increased Thymic output

**Graphs**

1. **TRECs/10^6 T cells**

2. **Number of CD4+CD45RA+CD62L+T cell/µl of blood**

3. **Number of CD8+CD45RA+CD62L+T cell/µl of blood**

**Week of study**
Vaccination with A/PR/8/34 influenza virus

Week of study

CD8+CD62L+CD45RA- cells/µl blood

Haemagglutination inhibition Assay

Geo Mean HAI titre
IL-7 administered subcutaneously every 3 days over 21 days, so receiving 8 doses.

Repeated injections needed because of short half life of IL-7.
After improved formulation; what next

- No widespread dissemination to all over 65
- We need to understand why some older individuals who get a respiratory infection can resolve the disease quickly whilst in others it leads to pneumonia, or myocardial infarction and death or prolonged disease and frailty.
- We need a study to identify those who would benefit from treatment
Summary

• Clinical picture shows age related decline in immune function is of major importance
• Immunotherapy aimed at T cell arm may hold key

• But who should get the treatment and when are the next questions to answer.
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