Lutetium 177 labeled rituximab: opened gateway to better radioimmunotherapy

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- Side chain theory of immunity
- Antibodies - magic bullets 1899/1906

Therapy of Non Hodgkin’s Lymphoma (NHL)

Zevalin®
Ibritumomab tiuxetan labeled with Y-90

Bexxar®
Tositumomab labeled with I-131
Are antibodies really “magic bullets”?

**Therapy of Non Hodgkin lymphoma (NHL)**

- Rituximab (Rituxan®),
- Obinutuzumab (Gazyva™),
- Ofatumumab (Arzerra®),
- Ibritumomab tiuxetan (Zevalin®)

- NHL is sensitive to radiation
- can be curative in early stage NHL
Design of new radiopharmaceuticals

- Antibody selection
- Suitable radionuclide
- Formulation issues
- Stability issues
- Pre-clinical studies
- Clinical studies
Selection of antibodies

- Target?
- Receptor?
- Affinity?
- Immunogenicity?

Murine
Chimeric
Humanized
Human

- antibody fragments
- tumor pretargeting
- type of administration

Radioisotope selection

- Diagnosis?
- Therapy?

Properties?
Availability?

SPECT/PET?
Rituximab

B-cell

Rituximab

\( p\text{-SCN-Bn-DOTA} \)

\( p\text{-SCN-Bn-DTPA} \)

\( 1\text{B4M-DTPA} \)

\( ^{177}\text{Lu} \)
## Why $^{177}$Lu?

<table>
<thead>
<tr>
<th>Energy emitted</th>
<th>90 Yttrium</th>
<th>131 Iodine</th>
<th>177 Lutetium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta (2.3 MeV)</td>
<td>Beta (0.6 MeV)</td>
<td>Beta (max 0.5 MeV)</td>
<td>Beta (max 0.5 MeV)</td>
</tr>
<tr>
<td>Gamma (0.36 MeV)</td>
<td>Gamma 208 keV (11%)</td>
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<tr>
<td>Half-life</td>
<td>64 hours</td>
<td>8.04 days</td>
<td>6.71 days</td>
</tr>
<tr>
<td>Mean path-length</td>
<td>3.9 mm</td>
<td>1 mm</td>
<td>0.7 mm</td>
</tr>
</tbody>
</table>
Bifunctional chelating agents

**Rituximab:BFCA**

1:20

**p-SCN-Bn-DOTA**

**p-SCN-Bn-DTPA**

**1B4M-DTPA**
Conjugation

Lyophilisation

Lyophilized kits
Radiolabeling of kits & physicochemical evaluation

- reconstitution in 0.9% NaCl, in the presence of acetate ions at pH 7.0 with Lutetium-177 with specific activity of 555 GBq/mg, at room temperature
Radiolabeling with $^{177}\text{Lu}$ after reconstitution of lyophilisates

$^{177}\text{Lu}$-DOTA-rituximab

$^{177}\text{Lu}$-DTPA-rituximab

$^{177}\text{Lu}$-1B4M-DTPA-rituximab

- High radiochemical purity
Conclusion

- Lyophilized kits, ready to label with $^{177}\text{Lu}$
- Candidates for pre-clinical cell and animal studies
- Candidates for new ready to label rituximab for NHL therapy
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