

Lutetium 177 labeled rituximab: opened gateway to better radioimmunotherapy

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УНИВЕРЗИТЕТ
„ГОЦЕ ДЕЛЧЕВ“
ШТИП



4th Balkan Congress of
Nuclear Medicine

Paul Erlich



- 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

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Clinical Cancer Research 3281s

Original article

Phase I/II ⁹⁰Y-Zevalin (yttrium-90 ibritumomab tiuxetan, IDEC-Y2B8) radioimmunotherapy dosimetry results in relapsed or refractory non-Hodgkin's lymphoma

Gregory A. Wiseman¹, Christine A. White³, Michael Stabin, William L. Dunn¹, William Erwin², Magnus Dahlborg⁶, Andrew Raubitschek⁴, Kastyia Karvelis⁵, Timothy Schultheiss⁵, Thomas E. Witzig⁶, Richard Belanger⁶, Stewart Spies⁶, Daniel H.S. Silverman⁶, Judy R. Berlin⁶, Eric Ding⁶, Antonio J. Grillo-López²

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ORIGINAL REPORT

Lymphoma with ody¹

cases of NHL³ are diagnosed
lence of the disease now esti-
ntly, treatment alternatives for
L included only chemotherapy
liation. Unfortunately, relapsed
d remissions are less likely and
re of therapy. High-dose ther-

Home / December 6, 2014; Blood: 124 (21)

Phase I Study of 131-I-Tositumomab Radioimmunotherapy (RIT) in Patients with Relapsed or Residual CD20 Antigen-Expressing B Cell Lymphomas Following Autologous Hematopoietic Stem Cell Transplantation

Yang Liu, MD¹, Elise A. Chong, MD², Sigrid Berg, MD², Abass Alavi, MD³, Rodolfo Perini, MD⁴, Jakub Svoboda, MD², Sunita Dwivedy Nasta, MD², Anthony Mato, MDMSCE², and Stephen J. Schuster, MD³

Safety of Tositumomab and Iodine-131 ab (Bexxar) in B-Cell Lymphoma, After Rituximab

as Younes, Vinay Jain, Stewart Kroll, Jennifer Lucas, Donald Podoloff,



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?

Murine

➤ antibody fragments

Receptor?

Chimeric

➤ tumor pretargeting

Affinity?

Humanized

➤ type of administration

Human

Immunogenicity?

Radioisotope selection

Diagnosis?

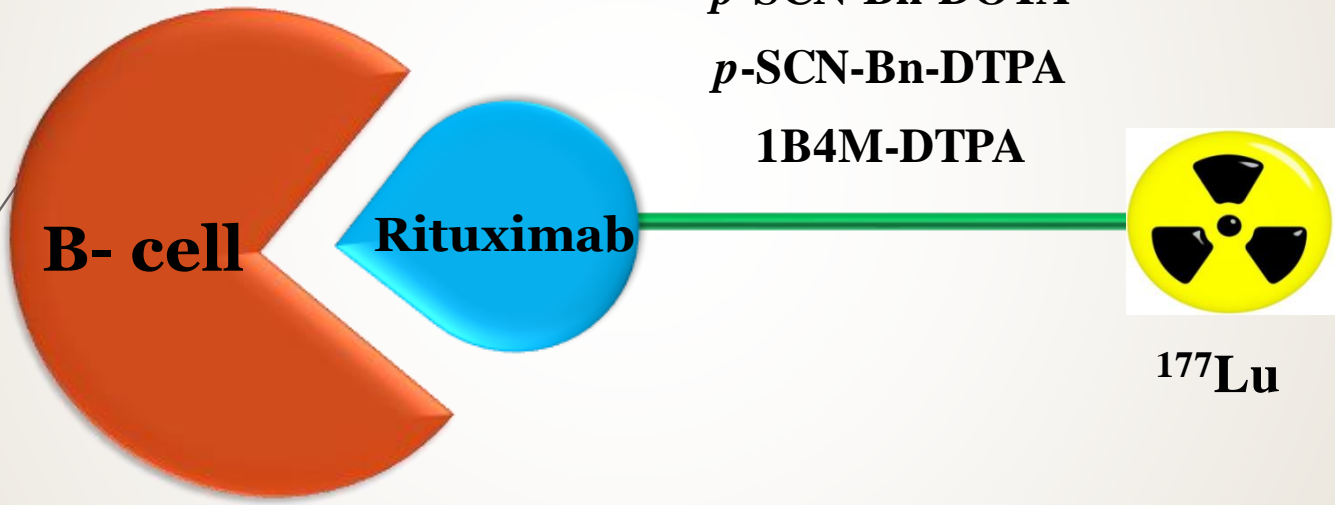
Properties?

SPECT/PET ?

Therapy?

Availability?

Rituximab



$p\text{-SCN-Bn-DOTA}$

$p\text{-SCN-Bn-DTPA}$

1B4M-DTPA

B- cell

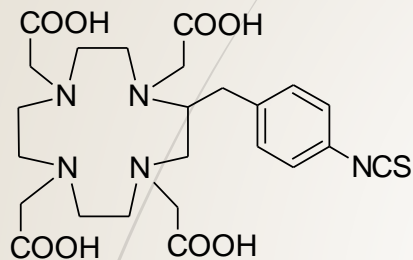
Rituximab

^{177}Lu

Why ^{177}Lu ?

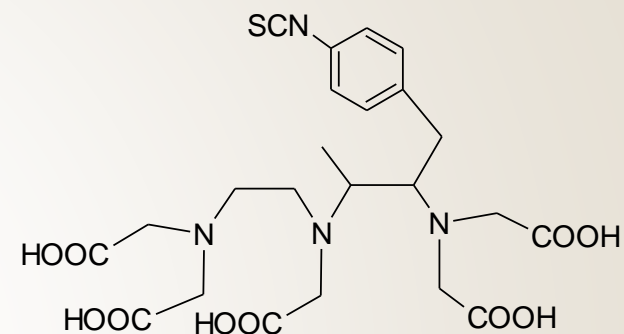
	90 Yttrium	131 Iodine	177 Lutetium
Energy emitted	Beta (2.3 MeV)	Beta (0.6 MeV) Gamma (0.36 MeV)	Beta (max 0.5 MeV) Gamma 208 keV (11%)
Half-life	64 hours	8.04 days	6.71 days
Mean path-length	3.9 mm	1 mm	0.7 mm

Bifunctional chelating agents



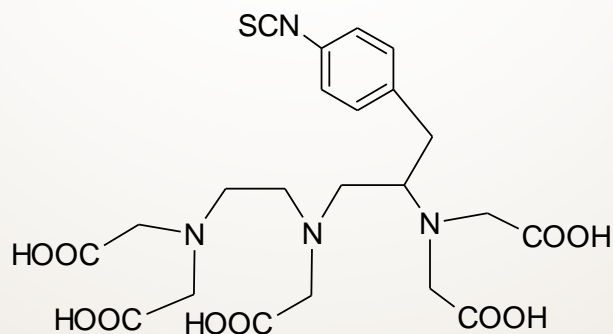
***p*-SCN-Bn-DOTA**

Rituximab:BFCA
1:20



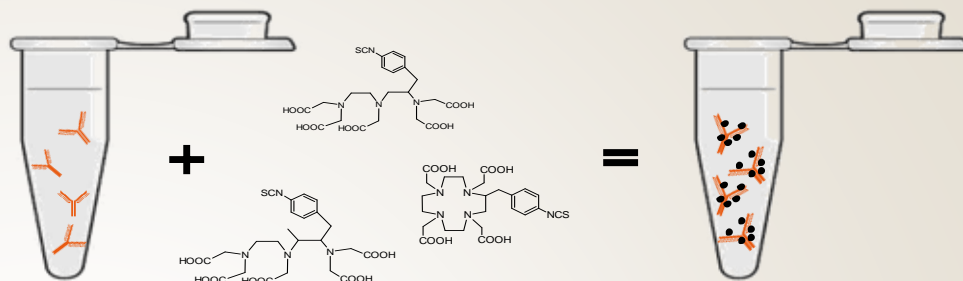
1B4M-DTPA

***p*-SCN-Bn-DTPA**

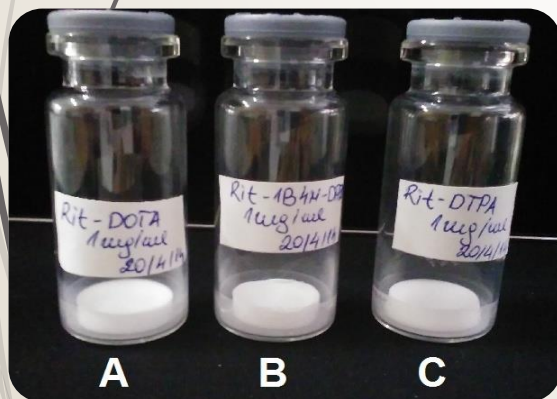




Conjugation



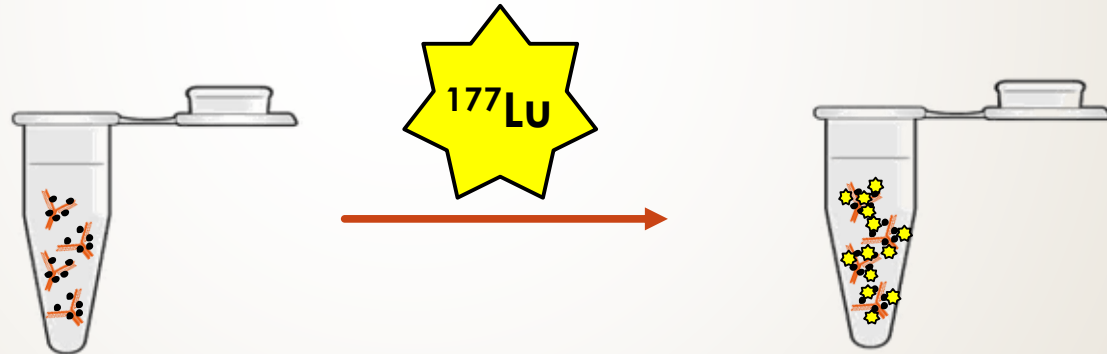
Lyophilisation



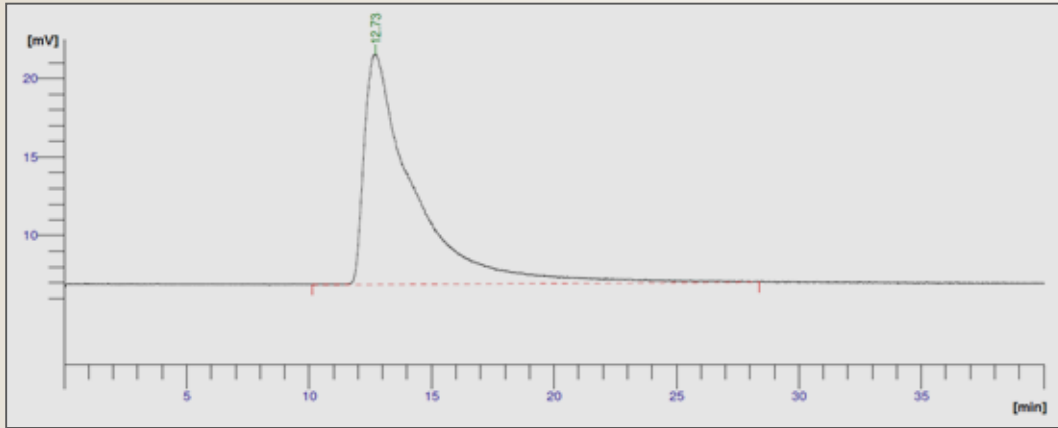
Lyophilized kits

Radiolabeling of kits & physicochemical evaluation

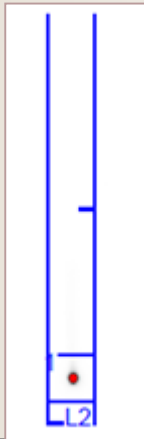
- ▶ reconstitution in 0.9% NaCl, in the presence of acetate ions at pH 7.0 with Lutetium-177 with specific activity of 555 GBq/mg, at room temperature



Radiolabeling with ^{177}Lu after reconstitution of lyophilisates



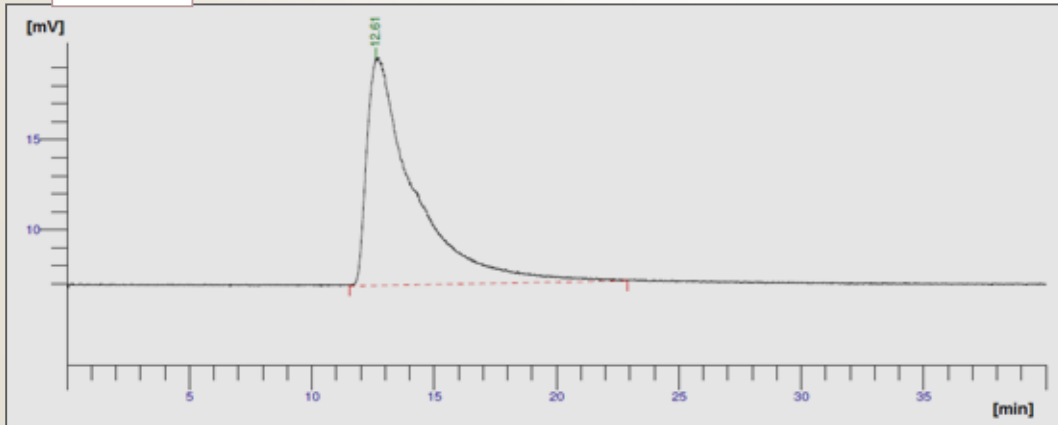
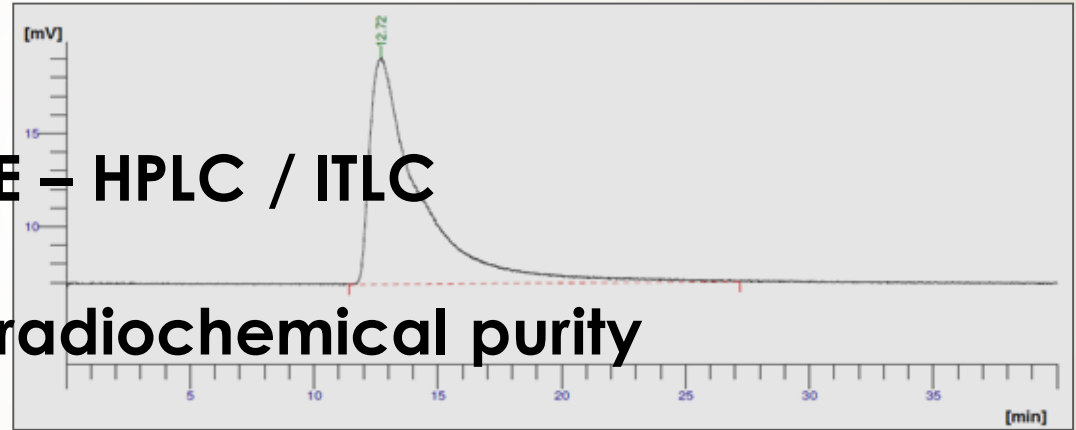
^{177}Lu -DOTA-rituximab



^{177}Lu -DTPA-rituximab

SE – HPLC / ITLC

➤ High radiochemical purity

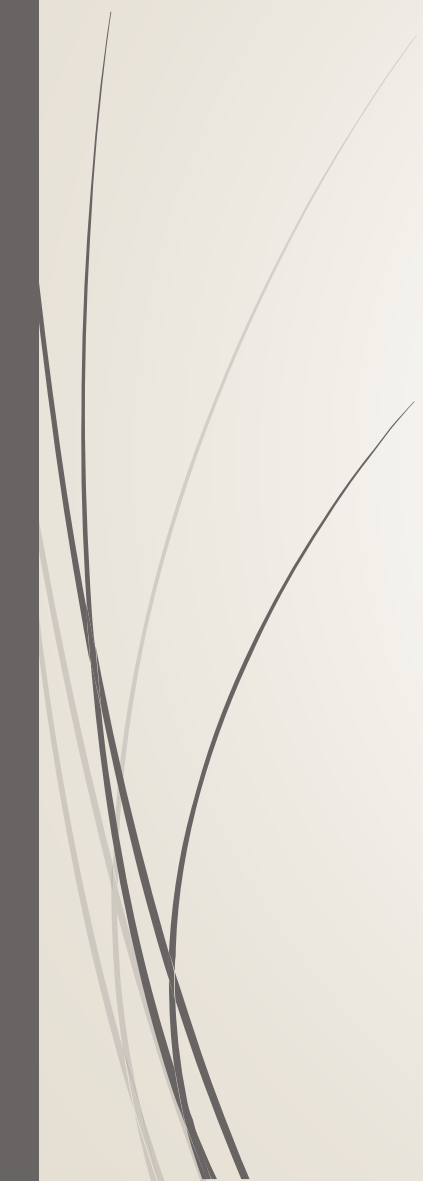


^{177}Lu -1B4M-DTPA-rituximab





Conclusion

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

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International Atomic Energy Agency