225Ac and 213Bi for radioimmunotherapy of cancer, infections and beyond

Ekaterina (Kate) Dadachova, Ph.D.

Professor of Pharmacy, Fedoruk Center for Nuclear Innovation Chair in Radiopharmacy

University of Saskatchewan, SK, Canada

Ever evolving Actinium…..

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Review

The coordination properties and ionic radius of actinium: A 120-year-old enigma

Gauthier J.-P. Deblonde *,[1], Mavrik Zavarin [2], Annie B. Kersting [3]

Glenn T. Seaborg Institute, Physical and Life Sciences Directorate, L-231, Lawrence Livermore National Laboratory, Livermore, CA 94550, United States

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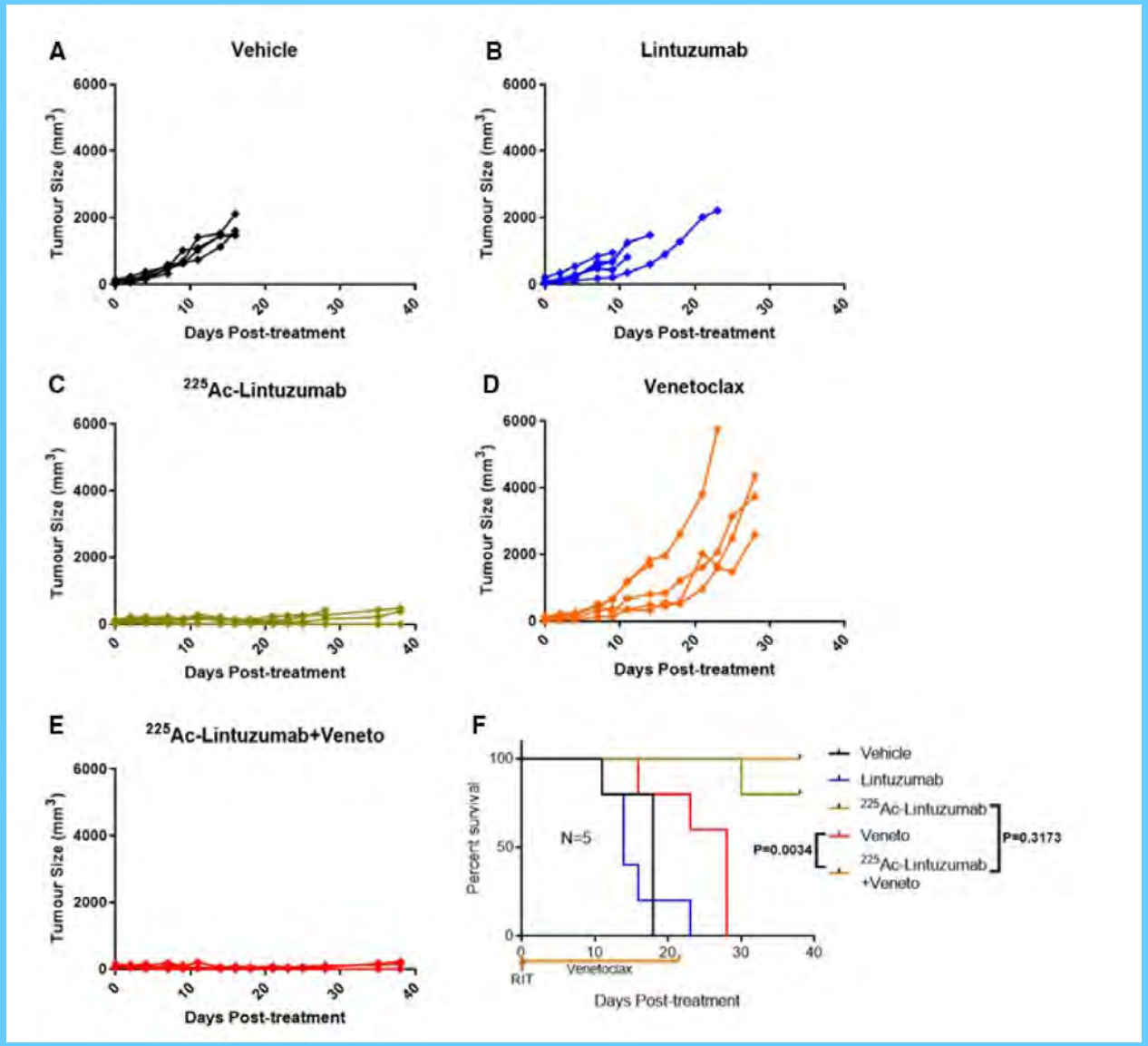
ABSTRACT

Actinium is an elusive element with untamed properties and represents a peculiar case in the periodic table, as its isotopes are all radioactive, the longest-lived one having only a 22-year half-life, and the availability of actinium isotopes remains very low (microgram level, at best), hindering research on its compounds. Despite being a natural element discovered more than 120 years ago, and despite an increasing interest in using one of its isotopes (^{225}Ac) for highly efficient cancer therapies, the chemistry of actinium is still largely unknown relative to other elements. Since Ac is the first element of the actinide series, it is accepted that its ion, Ac^{3+}, is the most voluminous trivalent cation of the periodic table. However, the structural data available on Ac^{3+} compounds are scarce and have mainly been collected in the 1940-1960′s, when actinide chemistry was still in its infancy, and have not been put in perspective with the advances in the chemistry of other elements, making it difficult to accurately evaluate its actual size and coordination chemistry. Herein, we review progress made on the chemistry of lanthanides and actinides and reevaluate the structural data published on Ac^{3+} since the era of the Manhattan Project. The data are combined across different spectroscopic and characterization methods and presented in the context of periodic trends. When considering crystallographic data, solution chemistry results, and the nuclear properties of actinium isotopes, it appears that some structural parameters ascribed to the Ac^{3+} ion may have been overestimated. This review can guide researchers interested in actinide sciences and those who are pursuing the development of actinium-based radiotherapies, from isotope production to clinical trials.

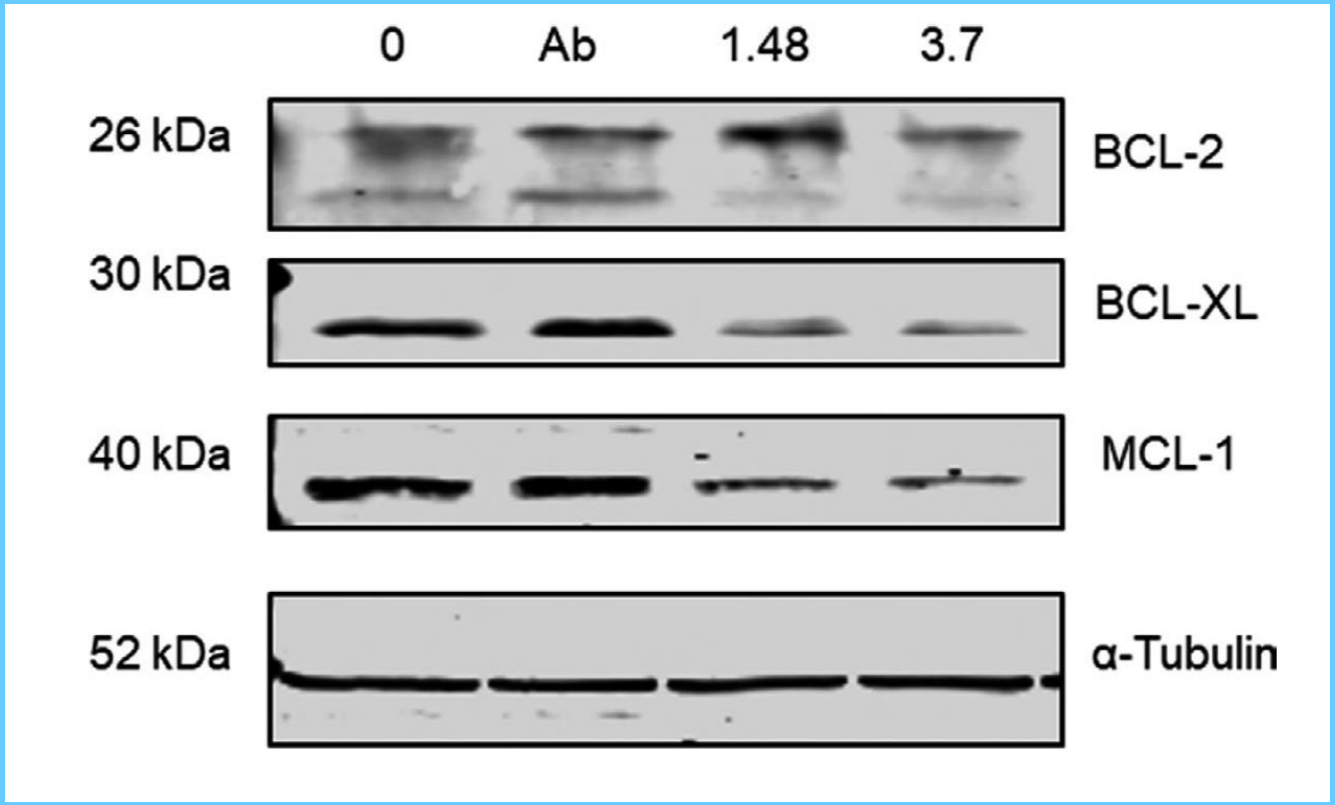
Actinium Pharmaceuticals, Inc.

^{225}Ac-labeled CD33-targeting lintuzumab and BCL-2 inhibitor venetoclax for radioimmunotherapy of acute myeloid leukemia (AML)

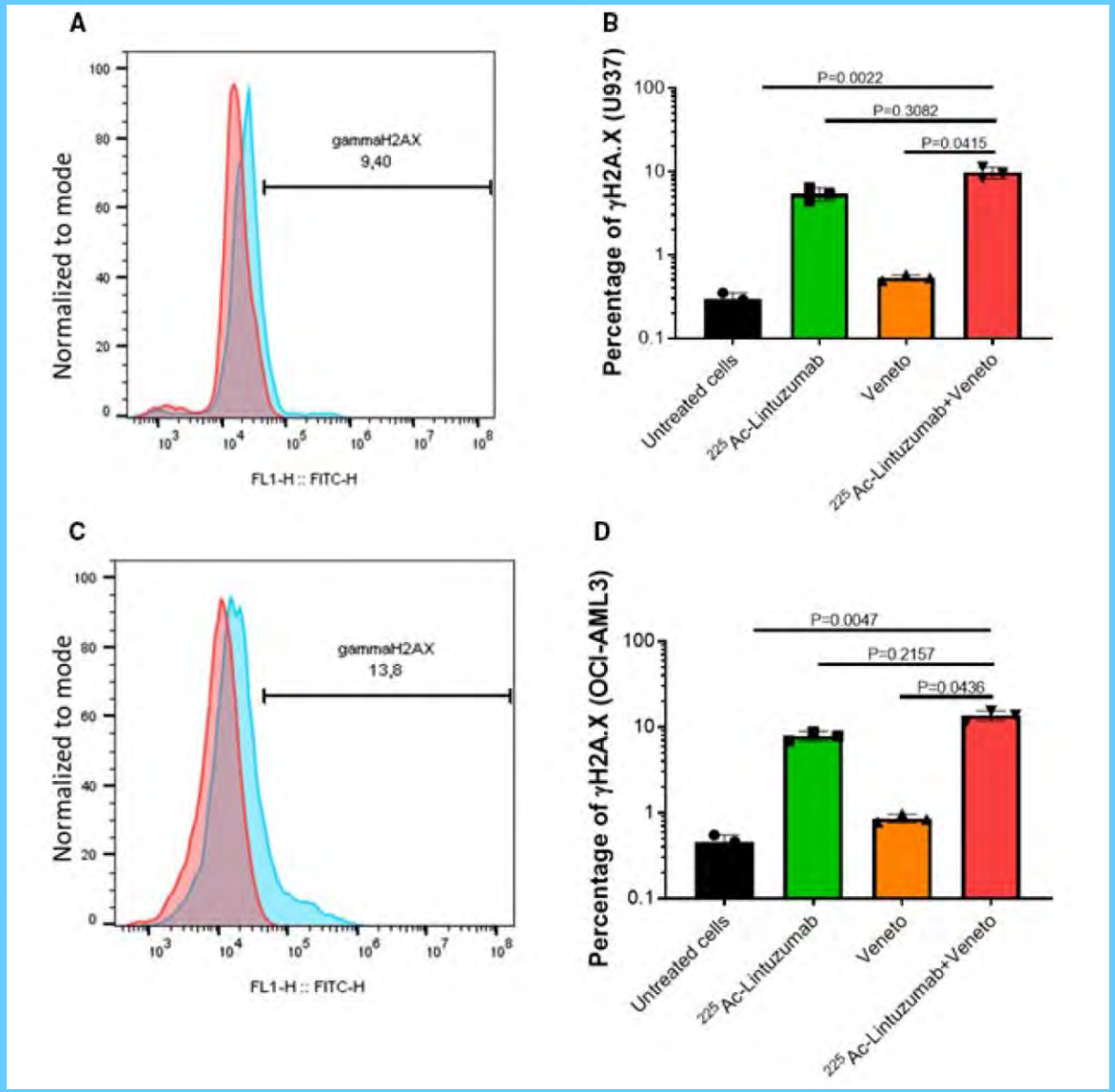
^{225}Ac-Lintuzumab and venetoclax combination provides a robust antitumor response and increases survival benefit in OCI-AML3 xenografts



^{225}Ac-lintuzumab downregulates the anti-apoptotic MCL-1, BCL-2, and BCL-XL protein levels in OCI-AML3 cells



^{225}Ac-lintuzumab induces double-stranded DNA breaks in AML cell lines



Garg R. et al. Cancer Med. 2021, Clinical trial NCT03867682 is ongoing

^{213}Bi-labeled antibodies to 1,3-beta-glucan for radiommunotherapy of fungal infections

Published in final edited form as:
Mycopathologia. 2012 June ; 173(0): 463–471. doi:10.1007/s11046-011-9476-9.

Toward Developing a Universal Treatment for Fungal Disease Using Radioimmunotherapy Targeting Common Fungal Antigens

R. A. Bryan,
Albert Einstein College of Medicine, 1695A Eastchester Rd., Bronx, NY 10461, USA

A. J. Guimaraes,
Albert Einstein College of Medicine, 1695A Eastchester Rd., Bronx, NY 10461, USA

S. Hopcraft,
Albert Einstein College of Medicine, 1695A Eastchester Rd., Bronx, NY 10461, USA

Z. Jiang,
Albert Einstein College of Medicine, 1695A Eastchester Rd., Bronx, NY 10461, USA

K. Bonilla,
Albert Einstein College of Medicine, 1695A Eastchester Rd., Bronx, NY 10461, USA

A. Morgenstern,
Institute for Transuranium Elements, Karlsruhe, Germany

F. Bruchertseifer,
Institute for Transuranium Elements, Karlsruhe, Germany

M. Del Poeta,
Medical University of South Carolina, Charleston, SC, USA

A. Torosantucci,
Istituto Superiore di Sanita, Rome, Italy

A. Cassone,
Istituto Superiore di Sanita, Rome, Italy

J. D. Nosanchuk,
Albert Einstein College of Medicine, 1695A Eastchester Rd., Bronx, NY 10461, USA

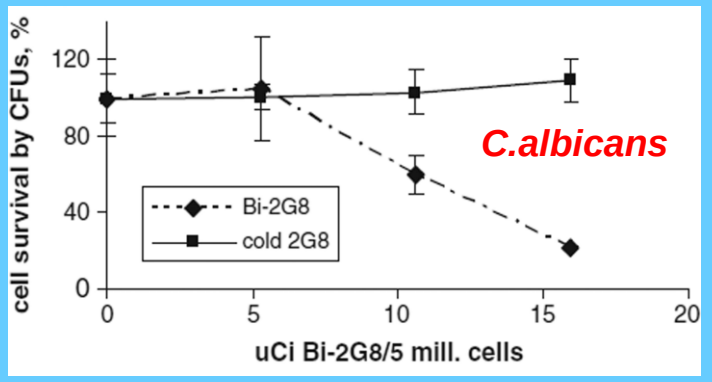
A. Casadevall, and
Albert Einstein College of Medicine, 1695A Eastchester Rd., Bronx, NY 10461, USA

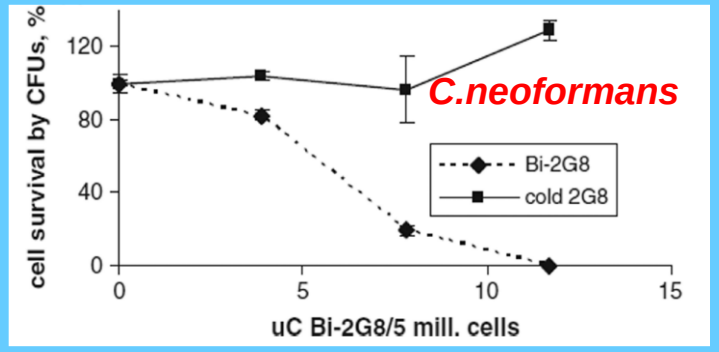
E. Dadachova
Albert Einstein College of Medicine, 1695A Eastchester Rd., Bronx, NY 10461, USA

E. Dadachova: ekaterina.dadachova@einstein.yu.edu

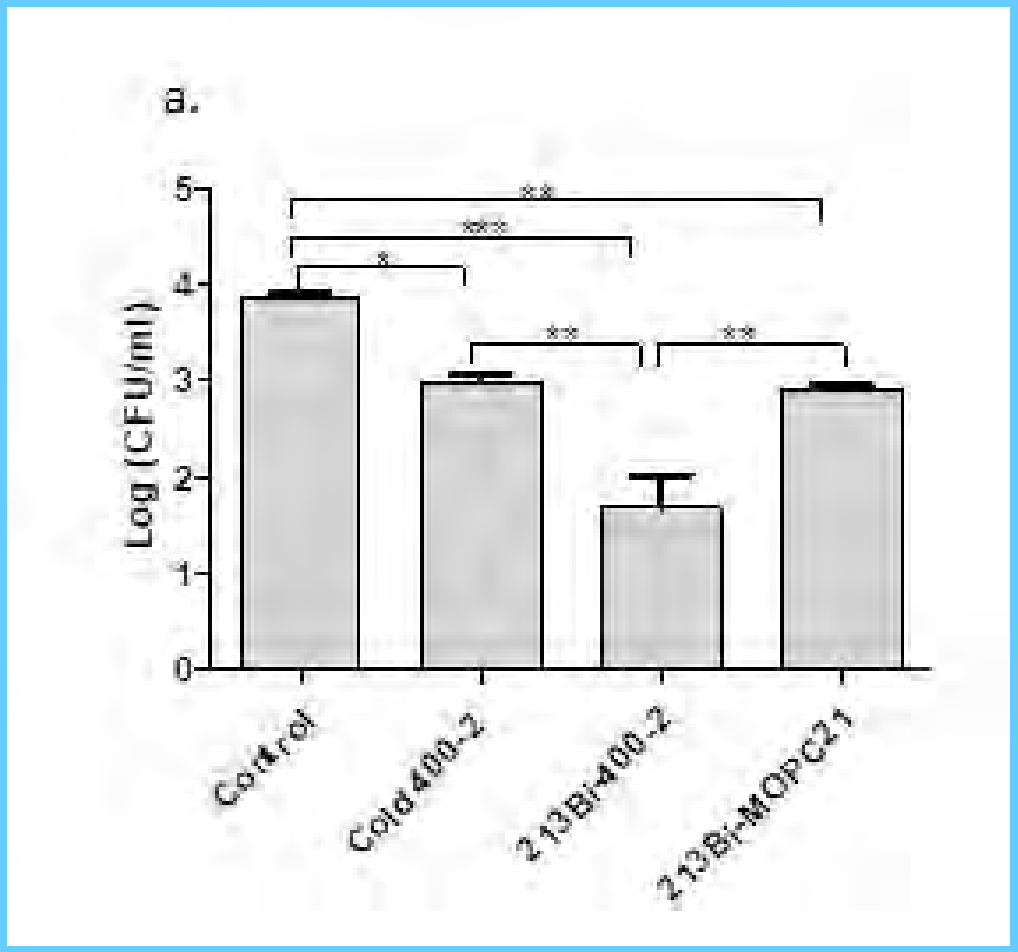
All human pathogenic fungi express:

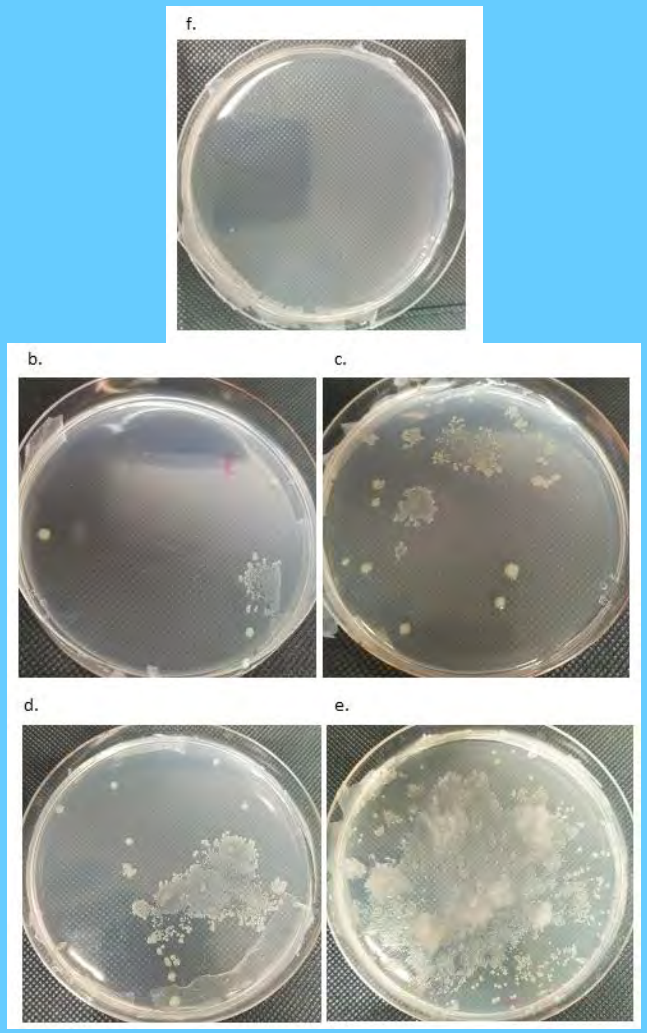
heat shock protein 60
beta (1,3)-glucan
ceramide
melanin





Treating mice infected with *Blastomyces dermatitidis* with RIT targeting beta-glucan

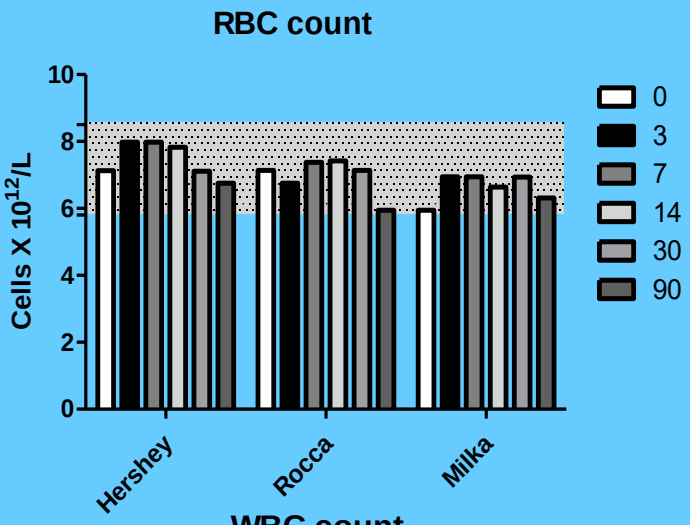


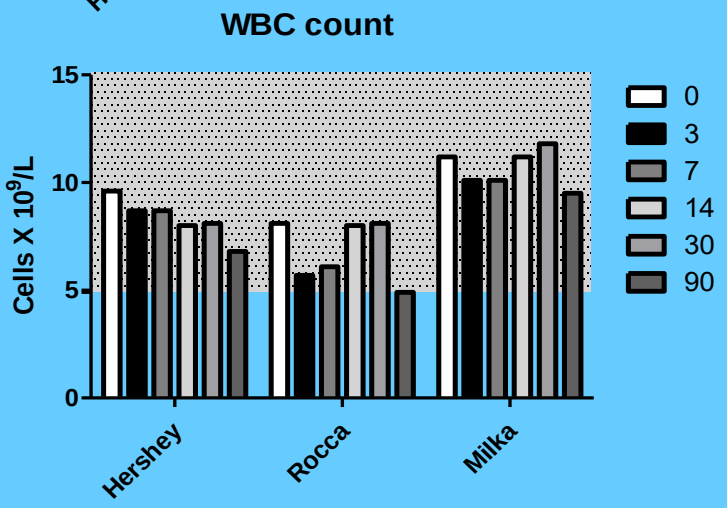


Helal M. et al. Front. Microbiol., 2020

Safety study of 213Bi-400-2 antibody in healthy dogs

Three 1.5 year old female beagles were given intraveniously 3.5 mCi 213Bi-400-2 (0.5 mCi/kg body weight).





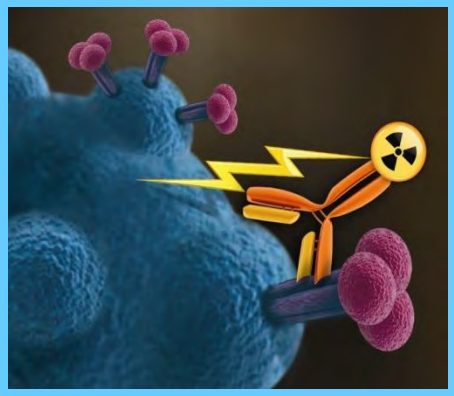
Helal M. et al. Molecules, 2020

^{213}Bi- and ^{225}Ac-labeled antibodies to HIV gp41 for radiommunotherapy of HIV

PLoS One. 2012;7(3):e31866. Epub 2012 Mar 9.

Pre-Clinical Evaluation of a ^{213}Bi-Labeled 2556 Antibody to HIV-1 gp41 Glycoprotein in HIV-1 Mouse Models as a Reagent for HIV Eradication

Ekaterina Dadachova[1]*, Scott G. Kitchen[2], Gregory Bristol[2], Gayle Cocita Baldwin[2], Ekaterina Revskaya[1], Cyril Empig[3], George B. Thornton[3], Miroslaw K. Gorny[4], Susan Zolla-Pazner[4,5], Arturo Casadevall[1]



High affinity

Ka = 0.1 nM,

3.6×10^6 binding sites per infected cell

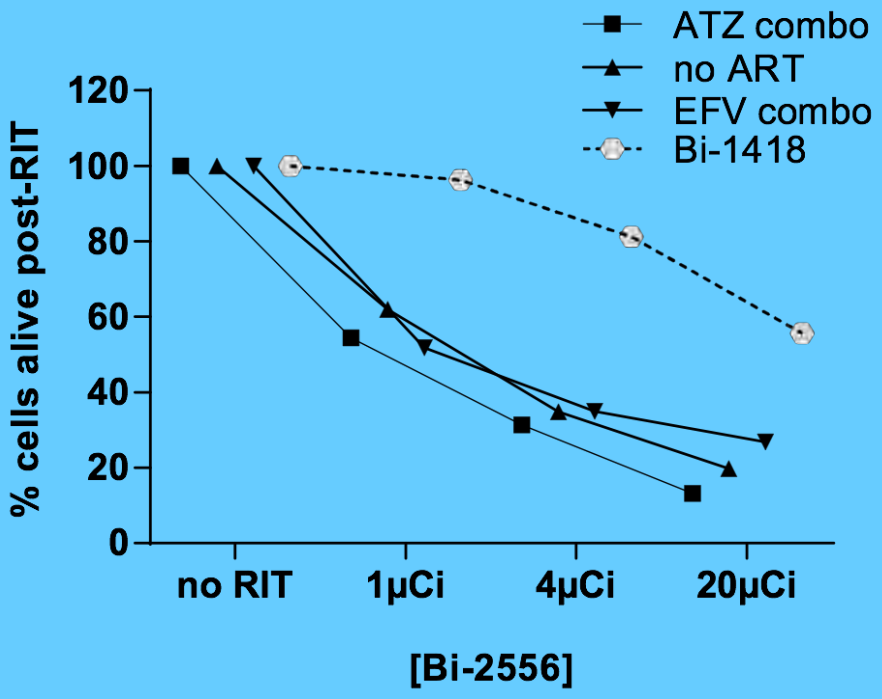
Targeted killing

Demonstrated *in vitro* and *in vivo* killing of infected human cells. **RIT reduced HIV to undetectable levels.**

Low toxicity

Platelet counts and gross pathology unaffected by RIT

RIT-induced killing of PBMCs derived from 15 ART-treated or ART-naive patients



Patient	0 μCi	4 μCi	20 μCi
ART- NAÏVE			
Well-controlled			
DT11	Not detected	Not detected	Not detected
DT15	31,860	50,770	35,355
Poorly-controlled			
DT04	44,702	18,300	13,883
DT08	257,040	108,735	5,480
DT09	113,670	138,075	4,425
TFV/FTC/EFV			
Well-controlled			
DT02	288	Not detected	Not detected
DT07	<400*	Not detected	Not detected
DT14	Not detected	250	Not detected
Poorly-controlled			
DT12	18,420	<400	Not detected
DT13	8,245	2,795	325
TFV/FTC/ATZ/RTV			
Well-controlled			
DT01	Not detected	Not detected	<400*
DT05	310	Not detected	Not detected
DT06	Not detected	Not detected	Not detected
Poorly-controlled			
DT03	<400*	<400*	<400*
DT10	49,775	14,890	Not detected

Tsukrov D. et al. Frontiers Med. 2016

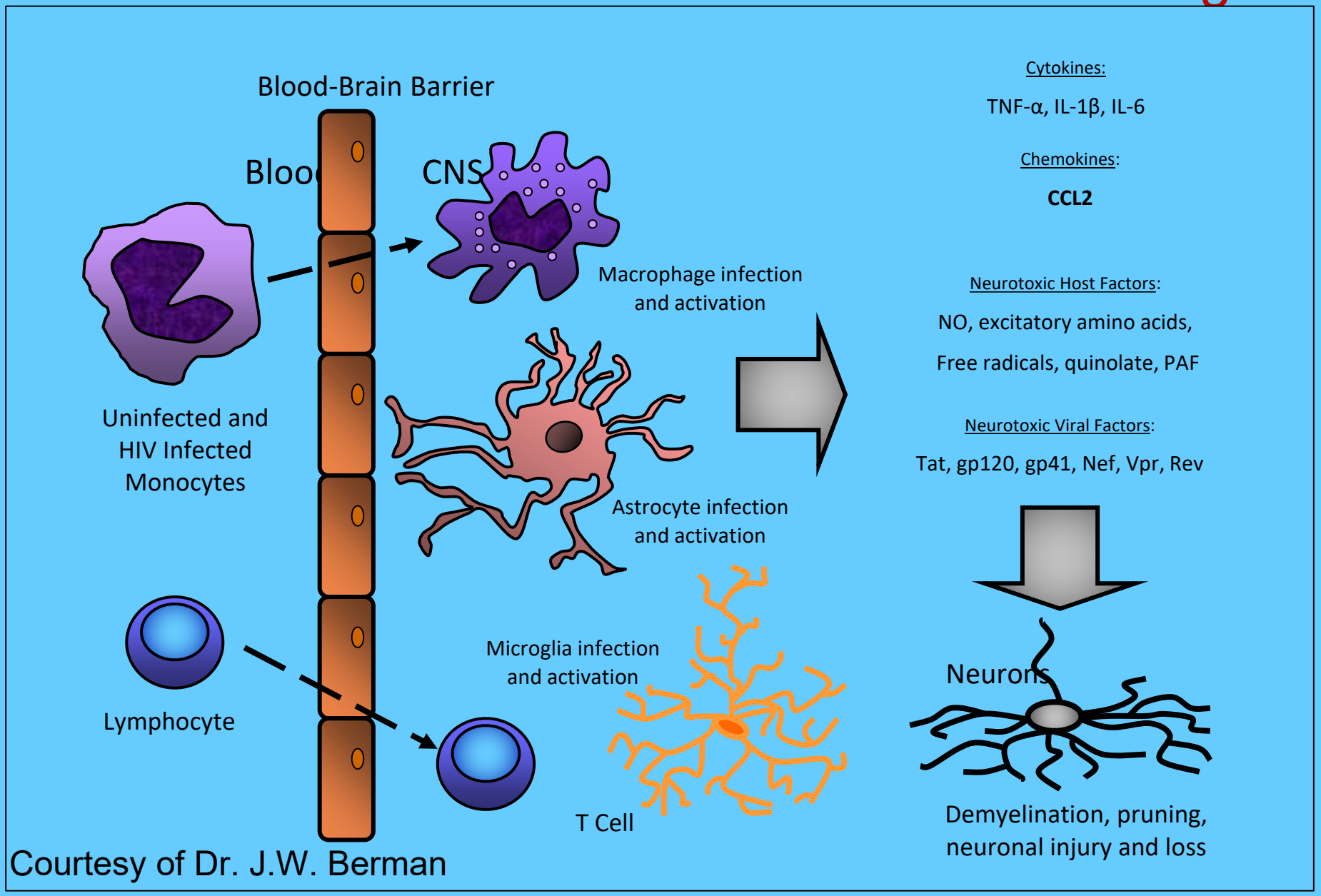
Another Kind of AIDS Crisis

A striking number of HIV patients are living longer but getting older faster —showing early signs of dementia and bone weakness usually seen in the elderly.

Left: **Cesar Figueroa**. Age: 50 / HIV: 20 years / Has suffered from: dementia, neuropathy, depression
Right: **Mike Weyand**. Age: 58 / HIV: 20 years / Has suffered from: osteoporosis, lipodystrophy, memory loss.
(Photo: Marco Grob)

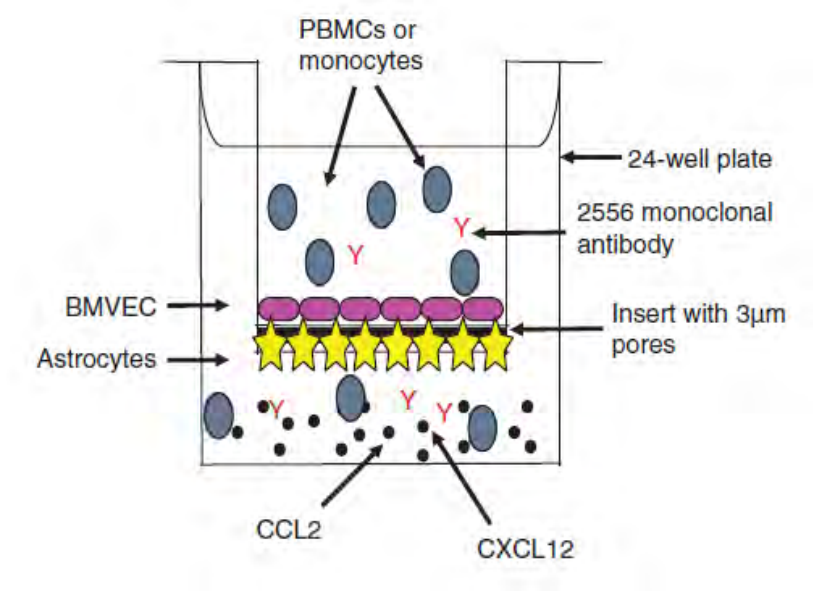
New York Magazine, 2009

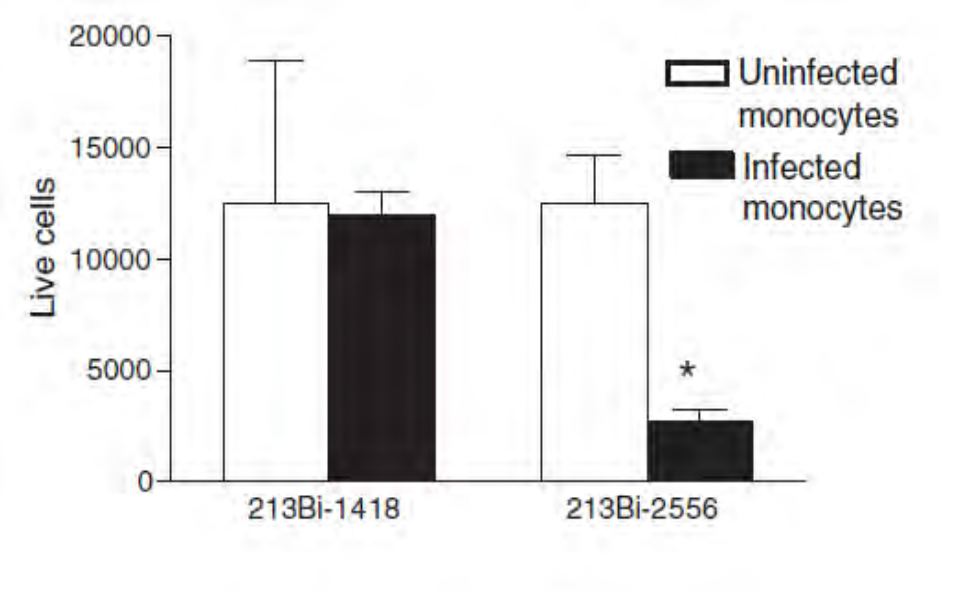
Mechanisms of CNS HIV Infection and Damage

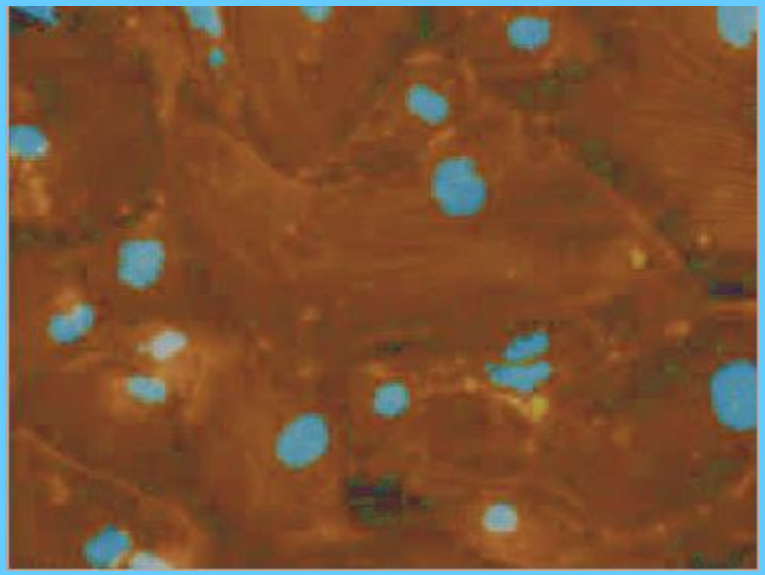


Courtesy of Dr. J.W. Berman

RIT induced killing of HIV-infected cells in human BBB model

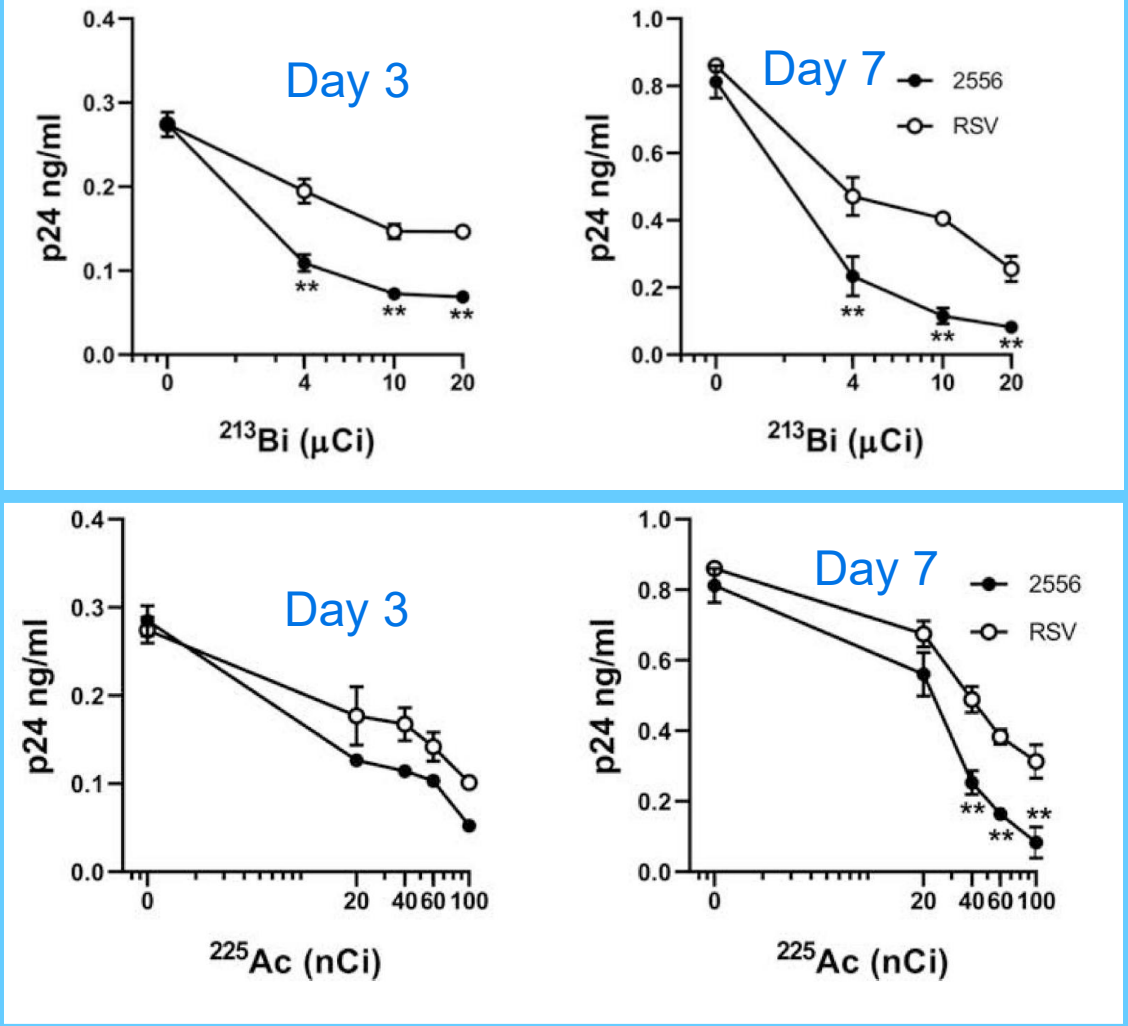






McFarren A. et al. AIDS 2016

^{213}Bi- and ^{225}Ac-labeled 2556 anti-gp41 antibodies are equally effective in killing HIV infected monocytes



Garg R. *et al.* Nucl. Med. Biol. *2020*

Next steps should be combination treatments in humanized mice and non human primates

Combination of ART, RIT and possibly, reactivation drugs in a state of the art humanized mouse model as a prelude to non-human primates studies.

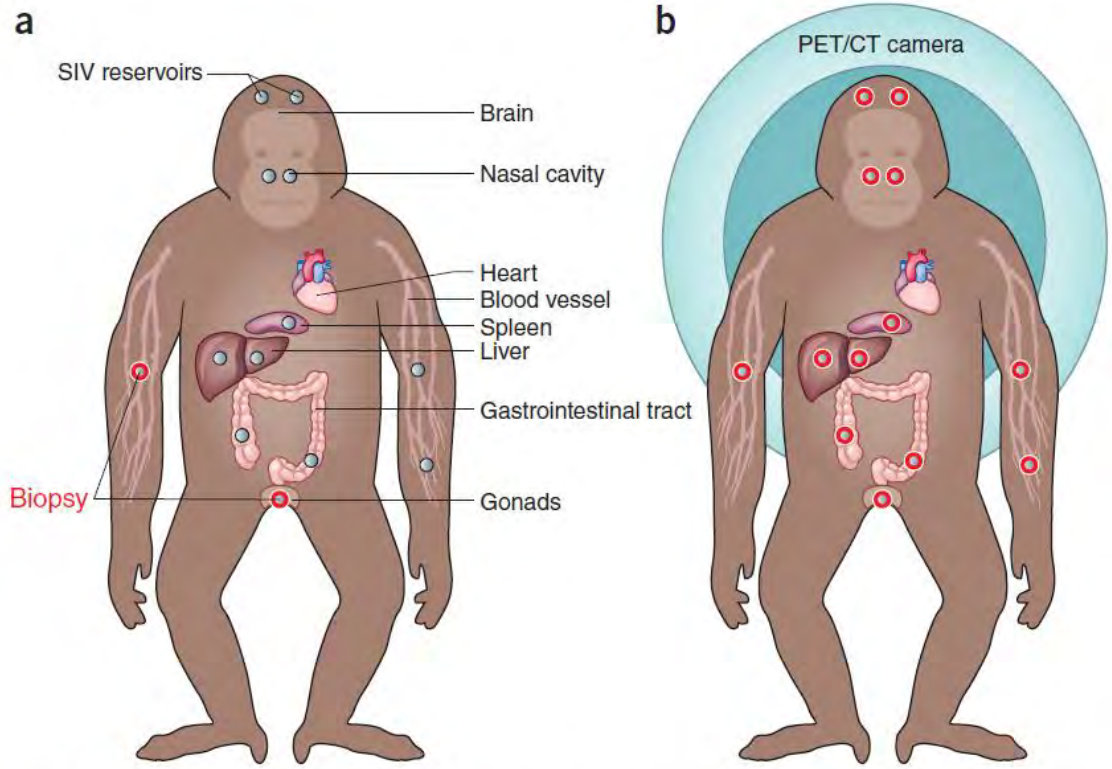


Figure 1 | Evaluating SIV reservoirs in monkeys. (**a**) Few SIV reservoirs (gray dots) can be easily reached and evaluated by biopsy (red circles). (**b**) SIV reservoirs can be comprehensively visualized and evaluated by immunoPET. CT, computed tomography.

Dadachova and Berman Nature Methods 2015

Next Frontier…

^{225}Ac and ^{213}Bi – labeled antibodies may be suitable for selective killing of cytotoxic T and B cells in autoimmune disorders such as diabetes, lupus and multiple sclerosis.

Conclusions

- Unique properties of ^{225}Ac and ^{213}Bi make them very attractive for treatment of cancer and infectious diseases.
- These radionuclides may also find applications for treatment of autoimmune disorders.
- Collaborations between researchers, physicians and industry partners are needed to bring those novel therapies to patients.

Thank you!

Dadachova's Lab
Mackenzie Malo
Kevin Allen
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Muath Helal
Kienna Mills

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Joshua Nosanchuk
Dina Tsukrov
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