Targeting DNA damage

Bart Cornelissen



Disclosures

- Theragnostics: paid consultancy and sponsored research
- Blue Earth Diagnostics: paid consultancy and contract research
- Honoraria from EANM, Novartis
- Patents on radiopharmaceuticals
- Employee of YMCG, honorary appointment at Oxford University

- Funding: CRUK, MRC, PCUK, PCR, OCIC. No involvement in research

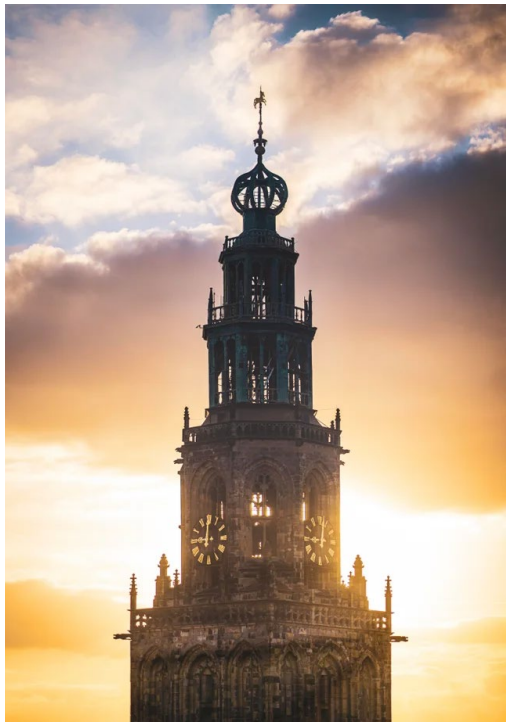












MSc radiochemie
PhD radiofarmacie

Postdoc

Assoc. Prof.
RPS
SRPS

Nuc Med boil
Radionuclide therapie
Kanker beeldvorming

Disclosures

- Open source: radiochemie
- Institute for Radiation Oncology and Biology: radiotherapie
- Radioaktieve materialen

- Scheikunde

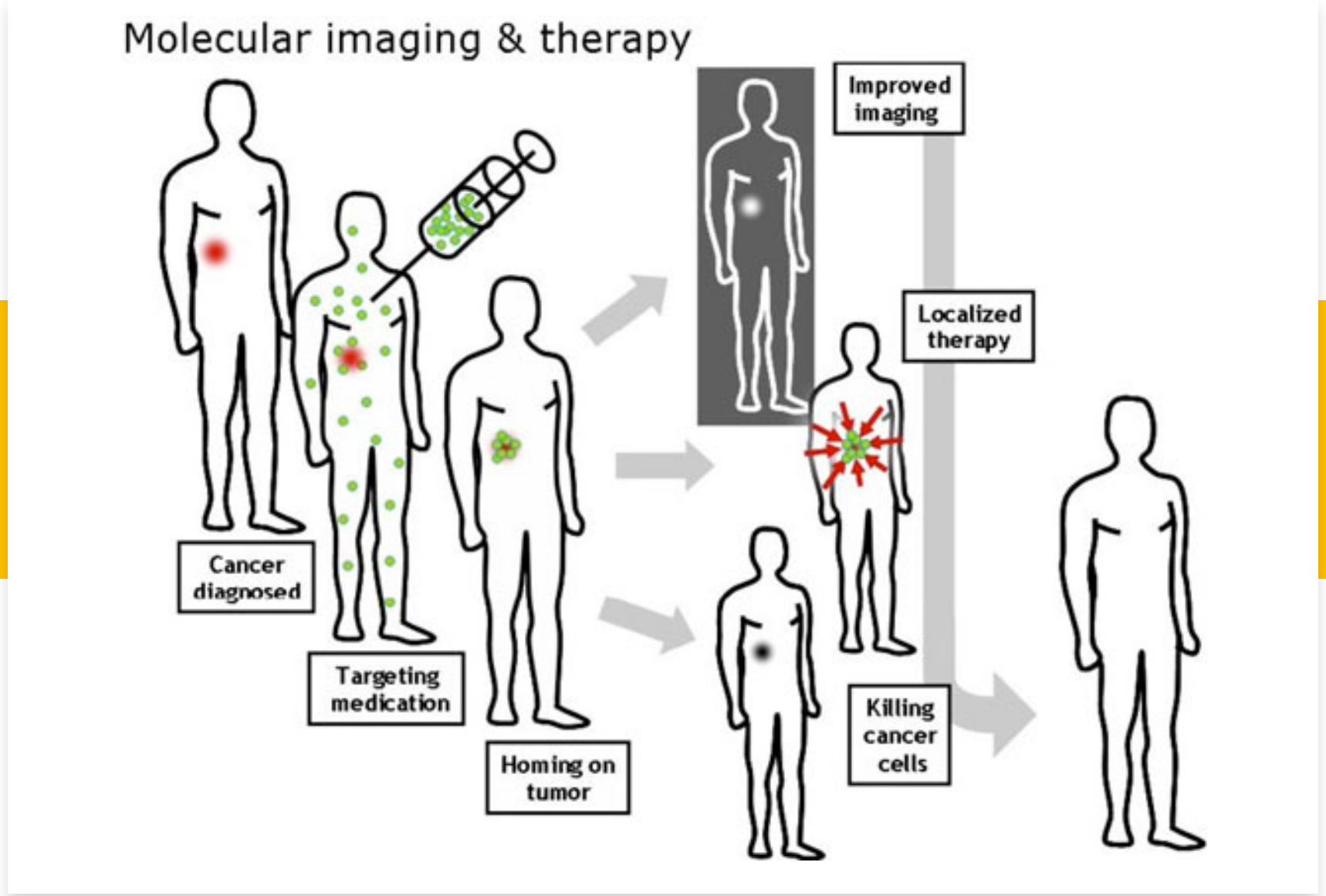
- I talk a lot (stop me….)

Inhoud

- Radiobiologie
  - Radiobiologie?
  - DNA schade
  - Visualisatie?
  - Radionucliden therapie?
- Research
- UK vs NL
  - Opleiding
  - Overzicht
  - Risicoanalyses

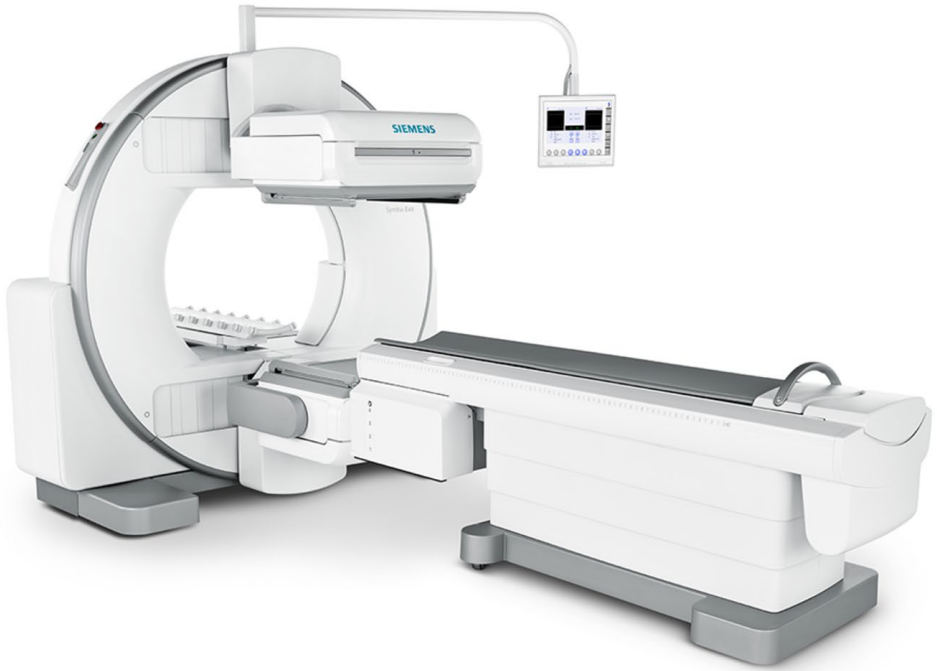


Anatomie vs. biologie



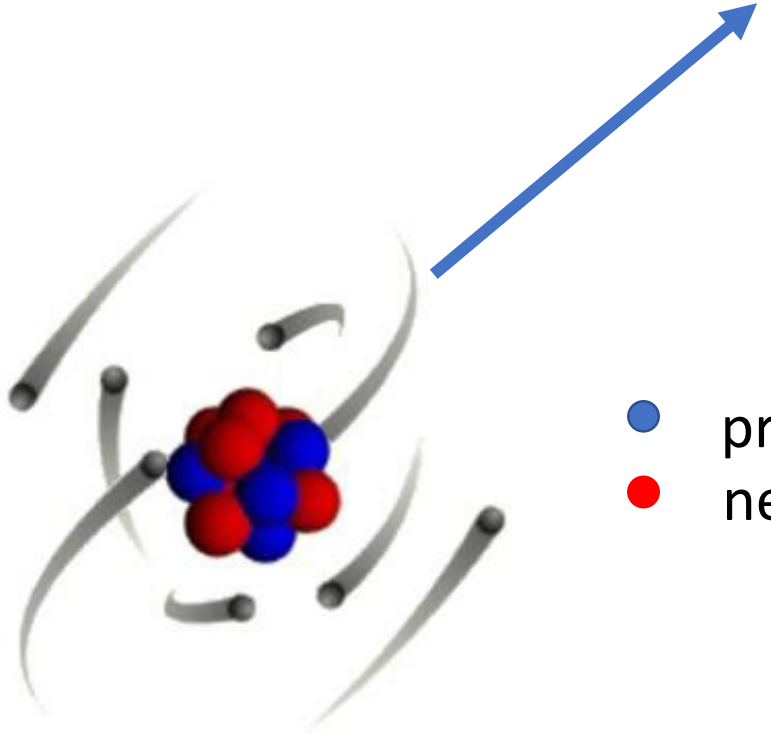
Nucleaire Geneeskunde, Moleculaire geneeskunde

Kliniek: SPECT en PET



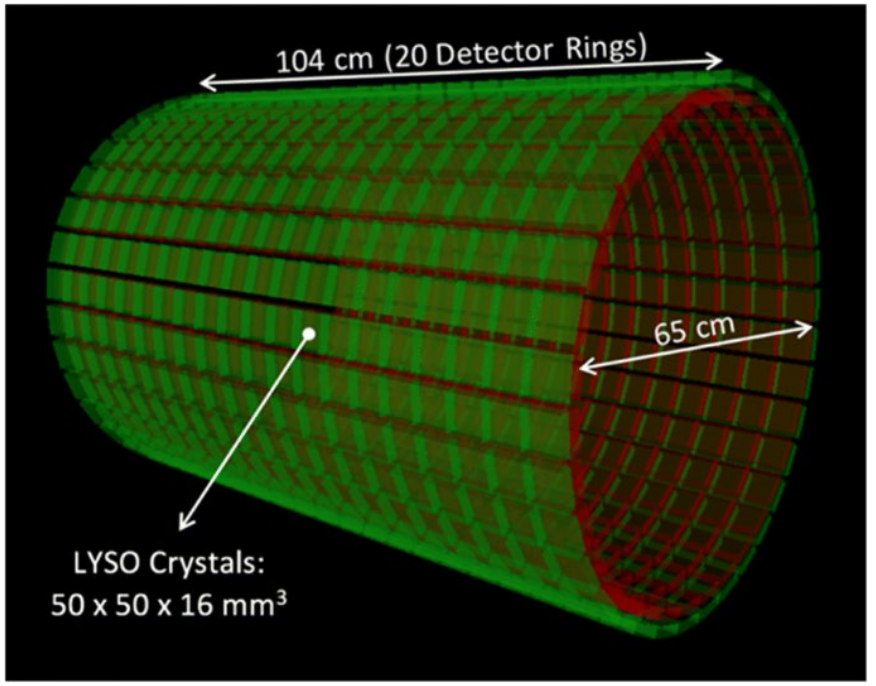


PET



proton

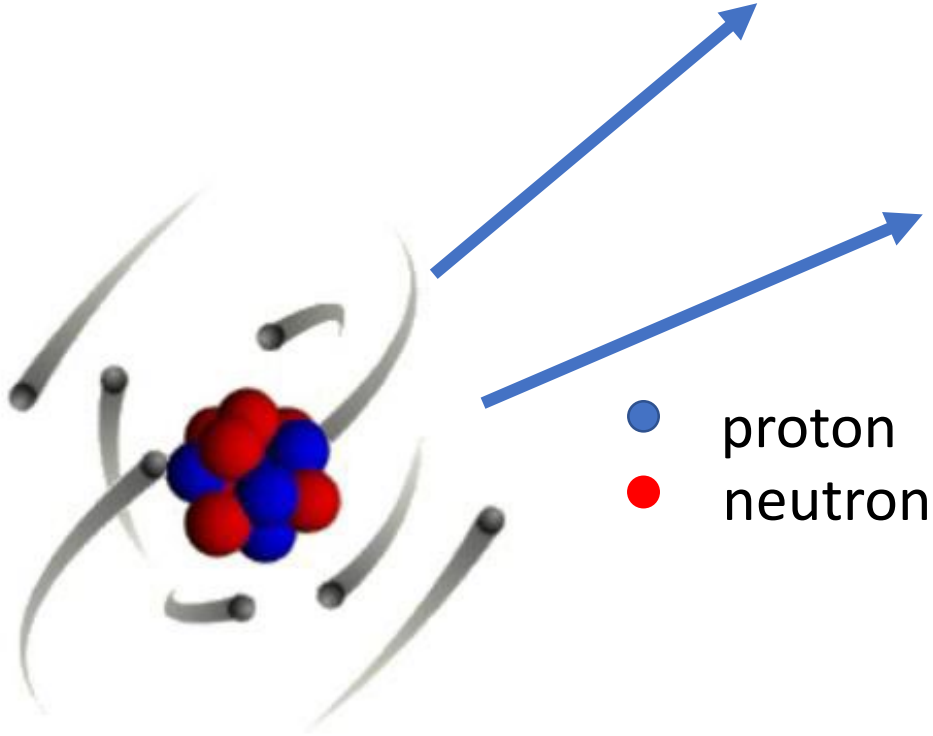
neutron



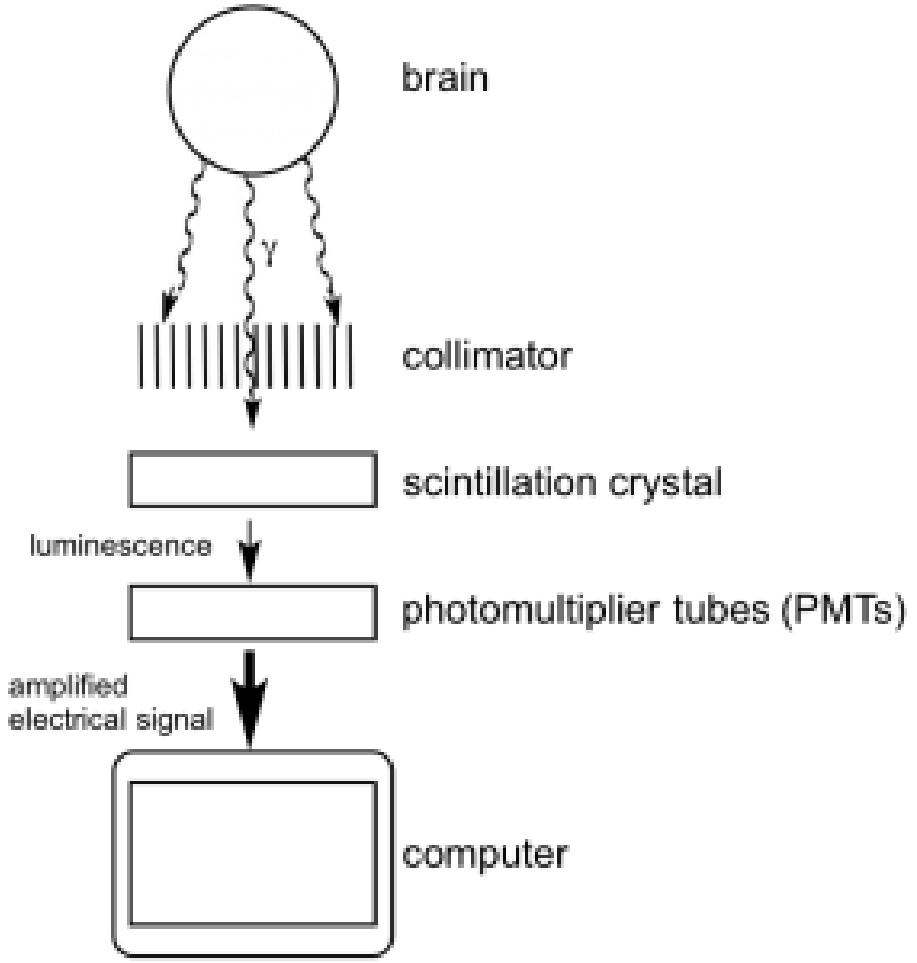
PET: ● → ● + positron → 2 gamma-rays ^{18}F (FDG), ^{89}Zr, ^{68}Ga

SPECT: 1, 2 gamma-ray ^{99m}Tc, ^{111}In, ^{123}I

SPECT



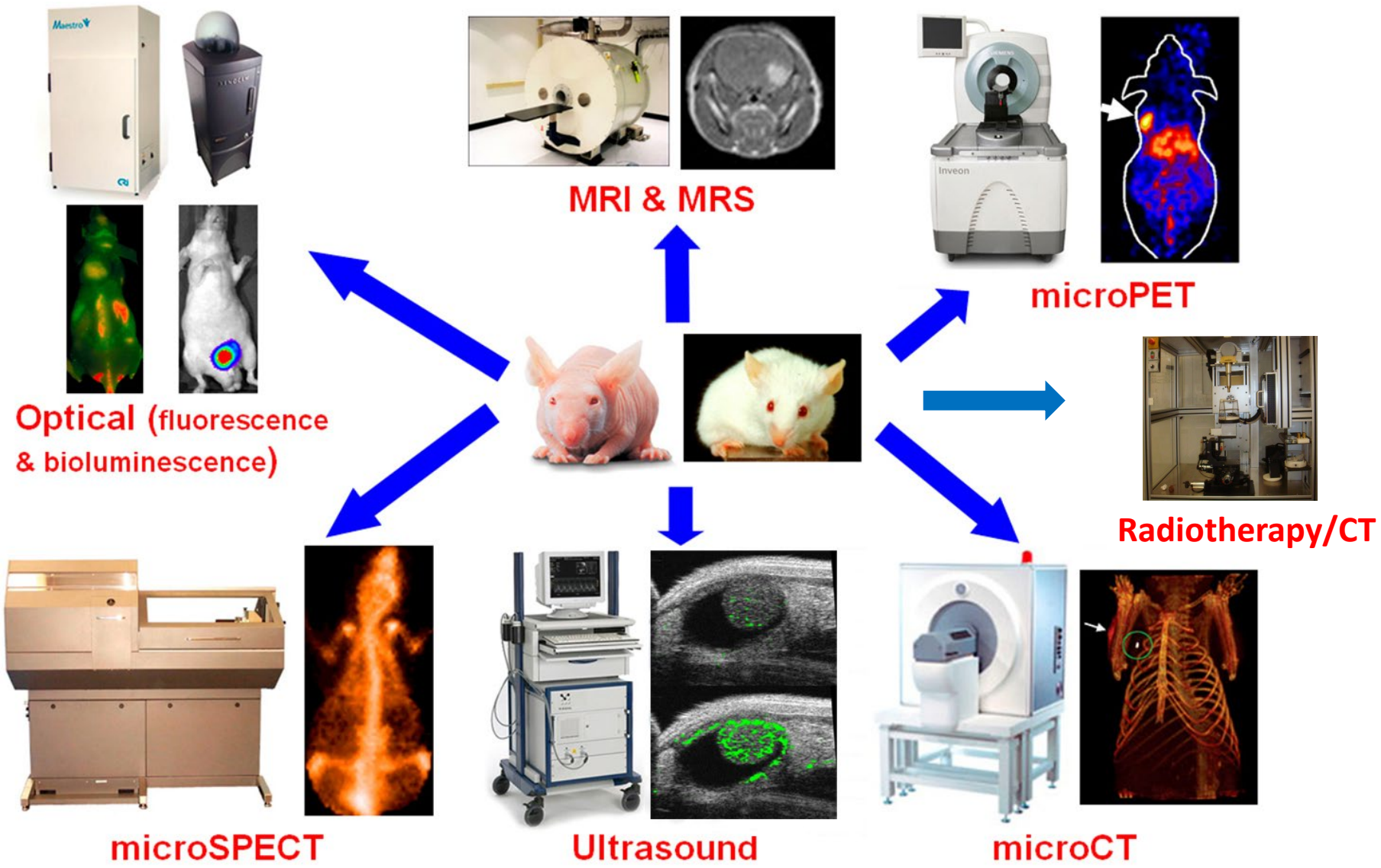
proton
neutron



PET: ● → ● + positron → 2 gamma-rays ^{18}F (FDG), ^{89}Zr, ^{68}Ga

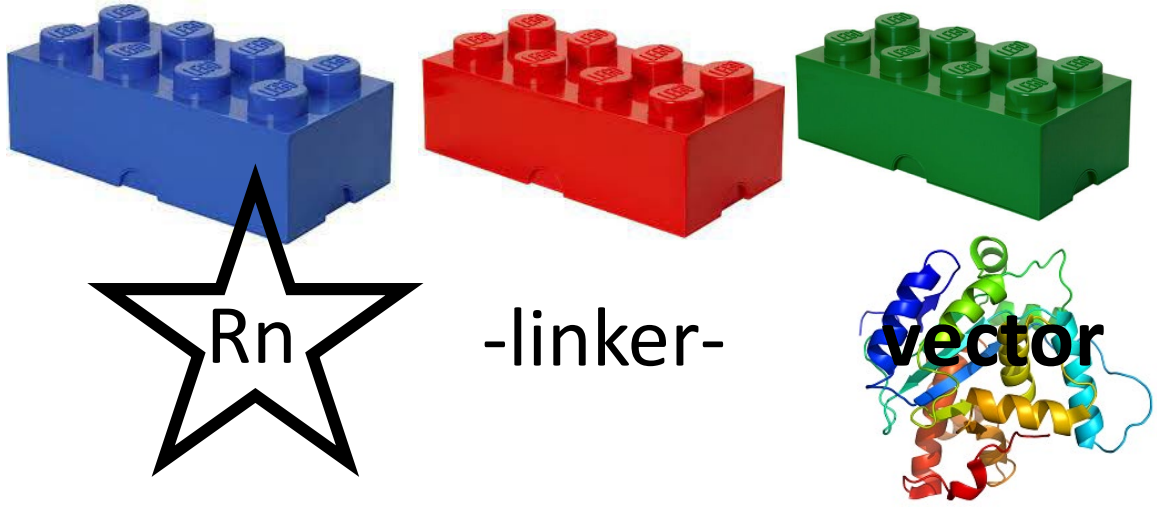
SPECT: 1, 2 gamma-ray ^{99m}Tc, ^{111}In, ^{123}I

What we do: Preclinical research: mini-versions

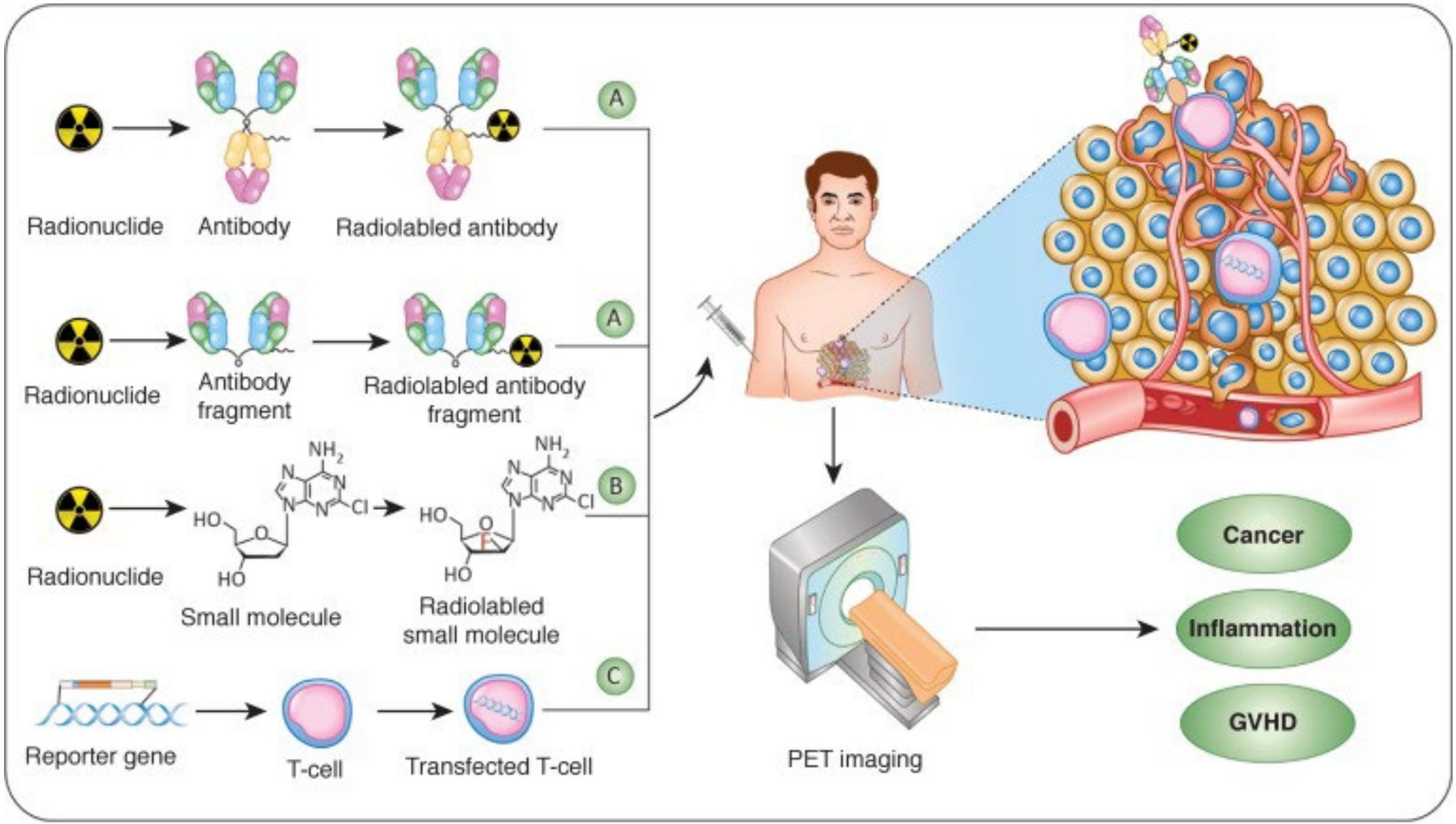


Radiopharmaca





Building a radiolabelled compound



Why measure DNA Damage Repair [DDR]?

- DDR after exo- and endogenous damage
- Genomic stability

  = Hallmark of Cancer
- Tumorigenesis

  mutations and genomic instability
- Image effects of therapy
  - radio & chemo
- Image tumorigenesis
  - early detection
- Prognostic marker?
- Radiosensitivity marker?
- Targeting -> Therapy
- Enhance to improve RLT

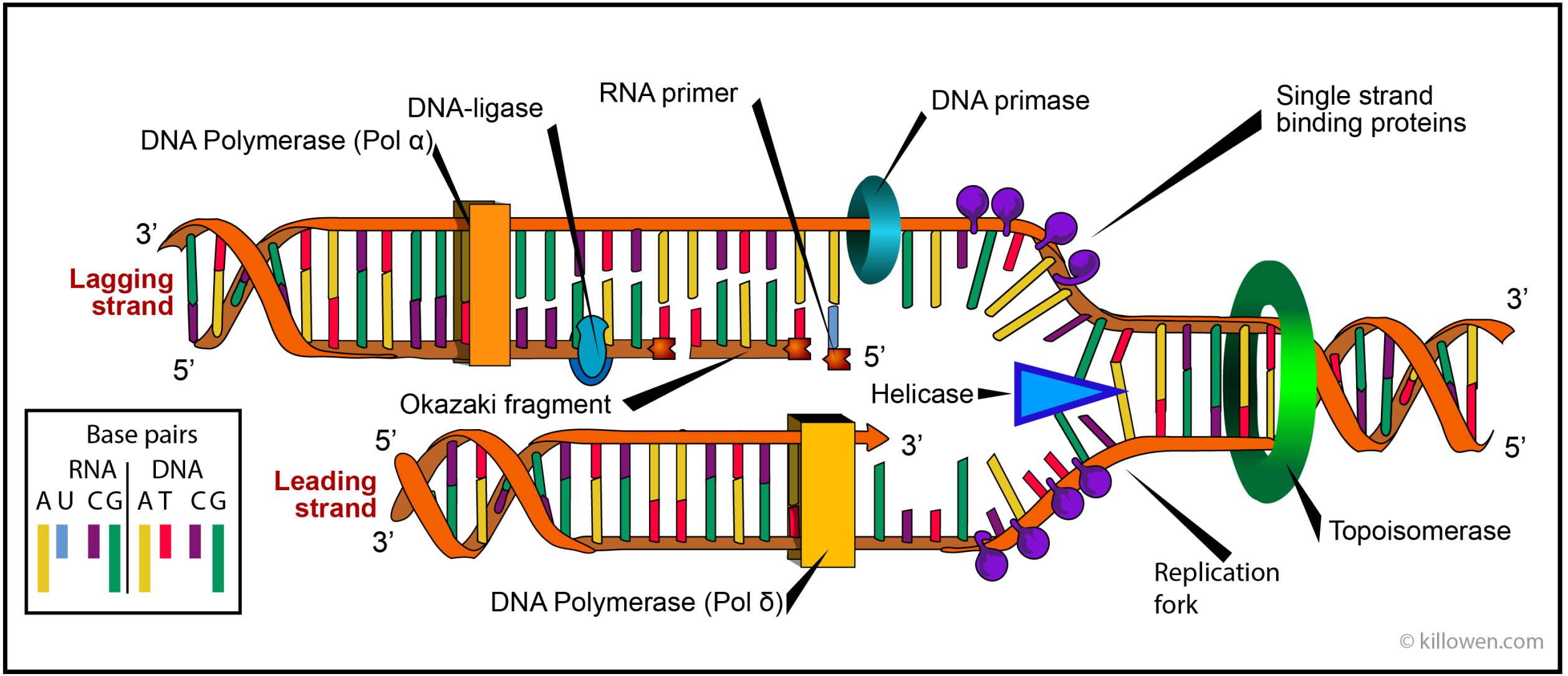


SSBs, DSBs en DDR

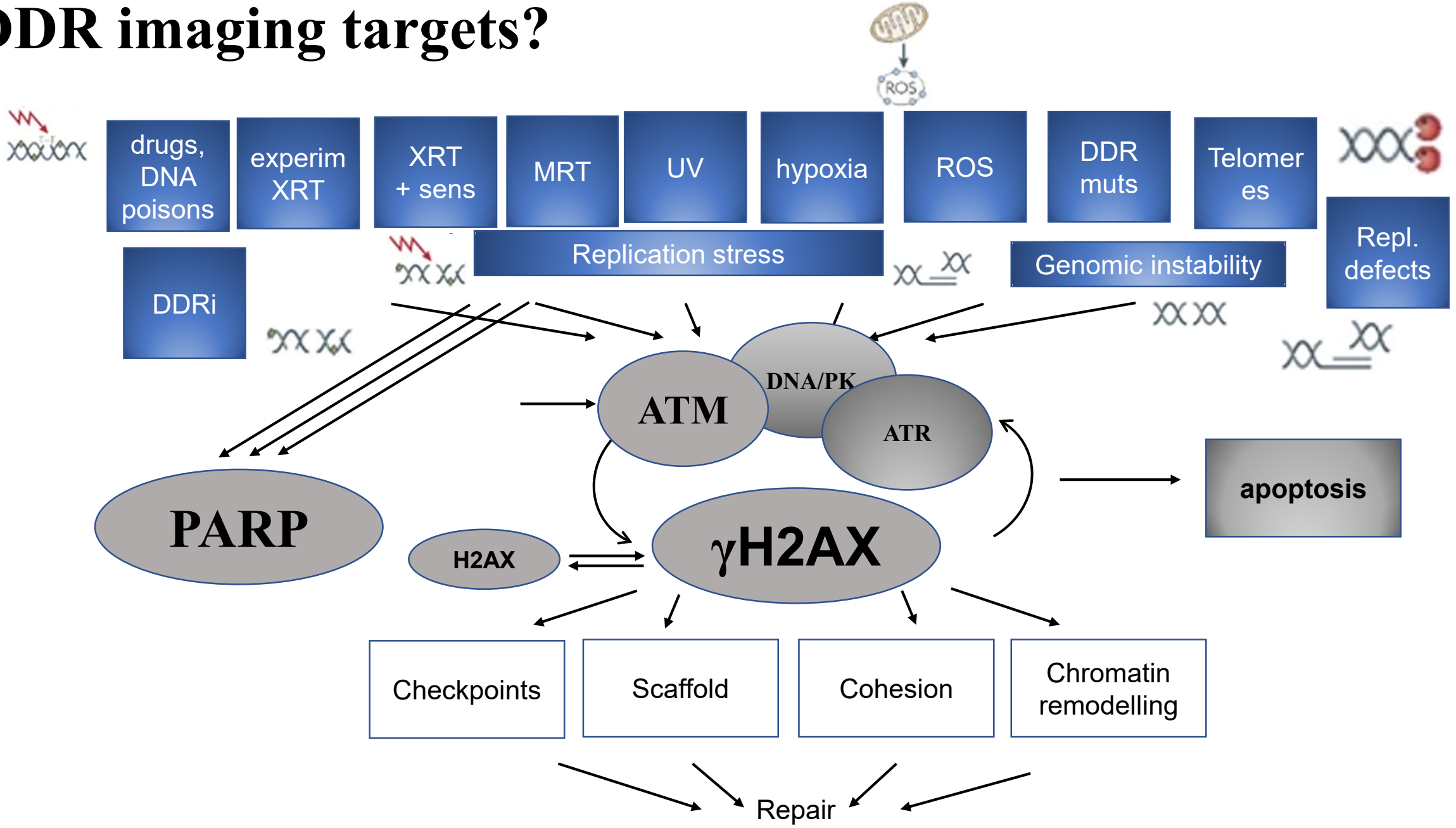




Replication fork



DDR imaging targets?

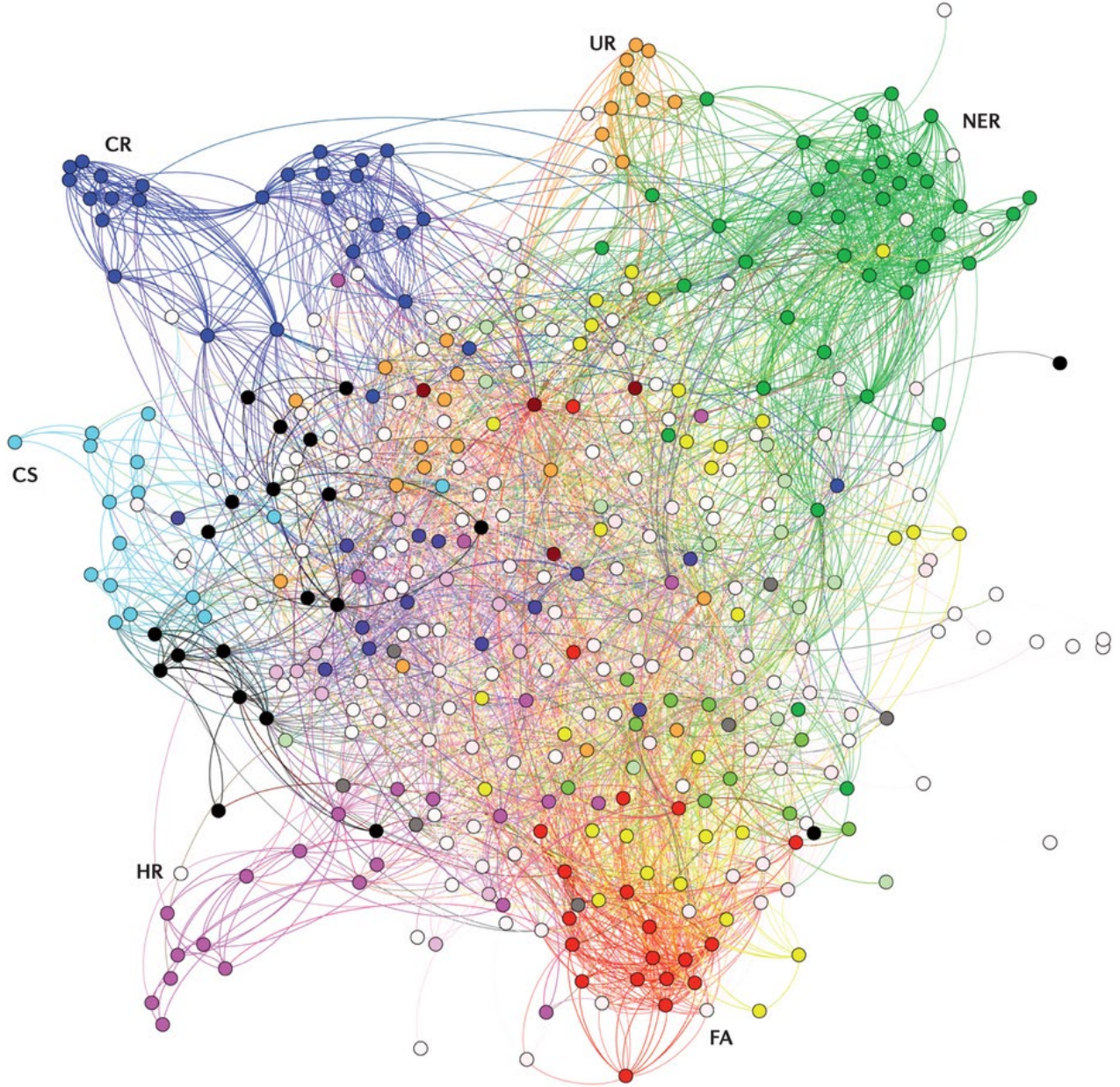


Bonner and Pommier Nat Rev Cancer 2008

Targets?

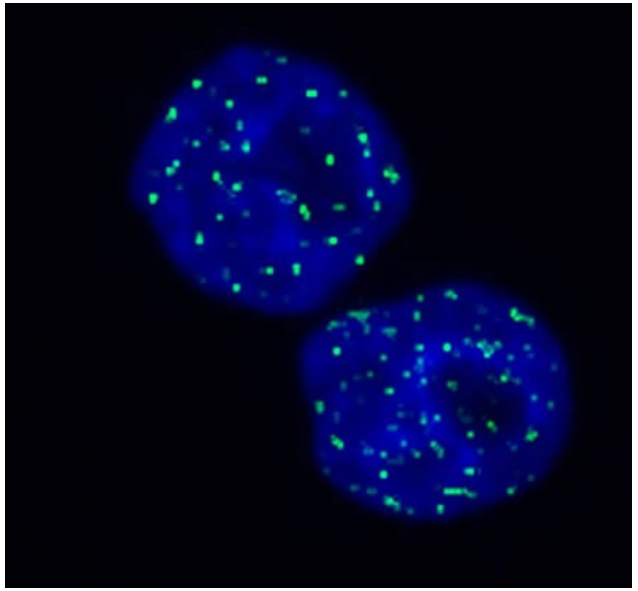
γH2AX

PARP

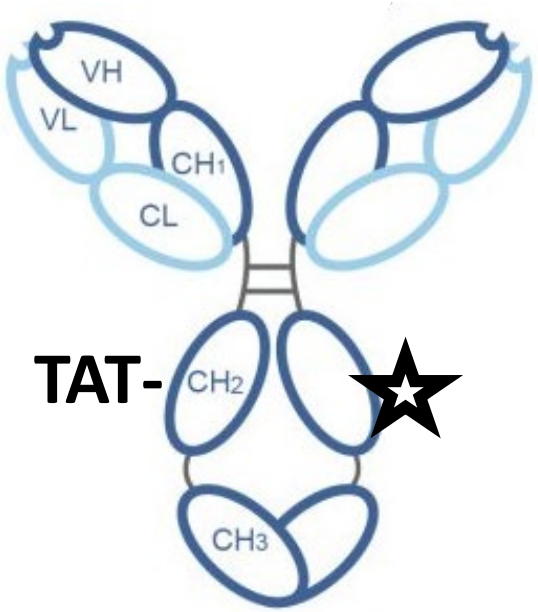


anti-γH2AX-TAT: non-invasive DSB imaging

γH2AX

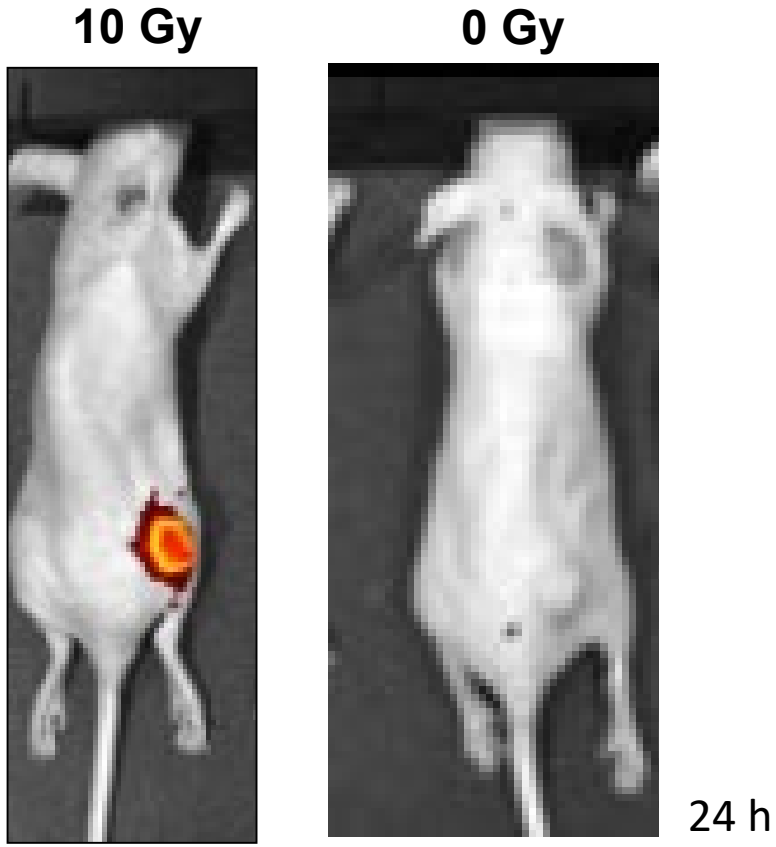


☆-anti-γH2AX-Tat



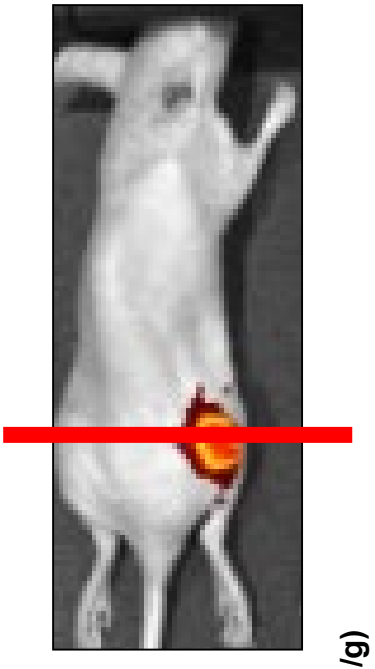


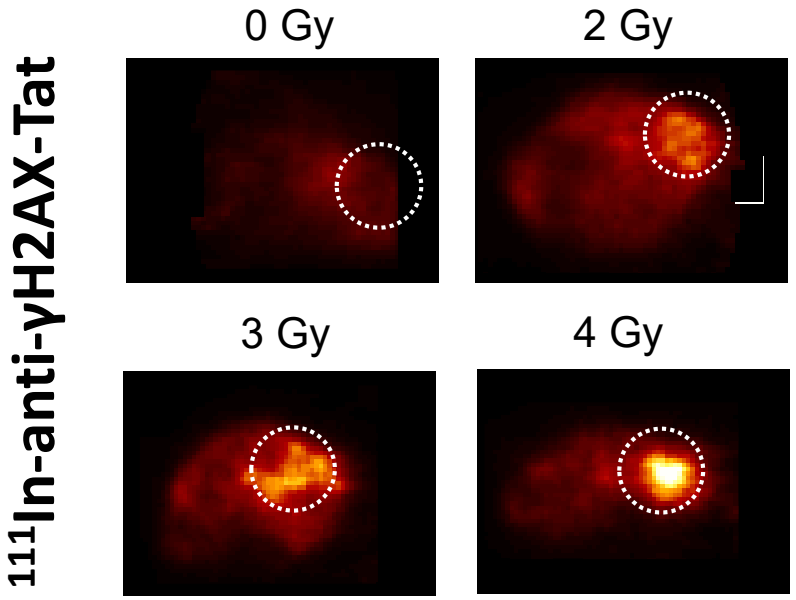
Cy3-anti-γH2AX-Tat

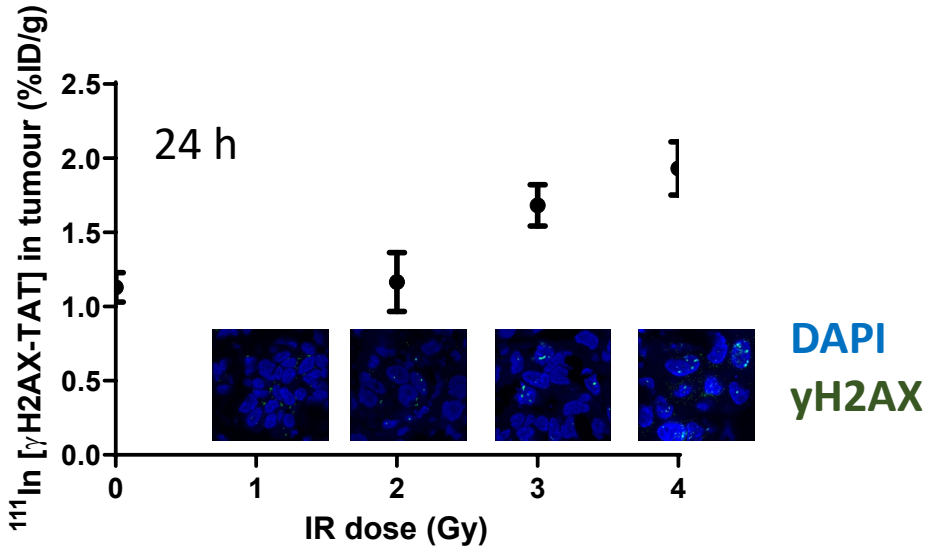


Cornelissen et al. Cancer Res 2011

Radiotherapy

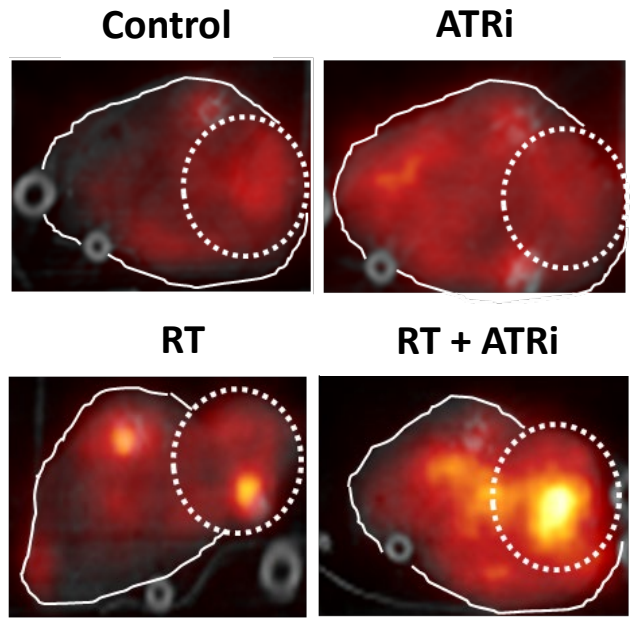


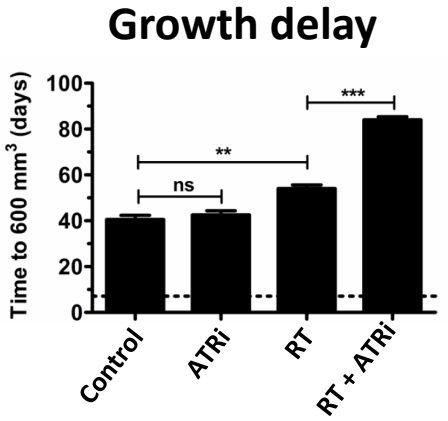


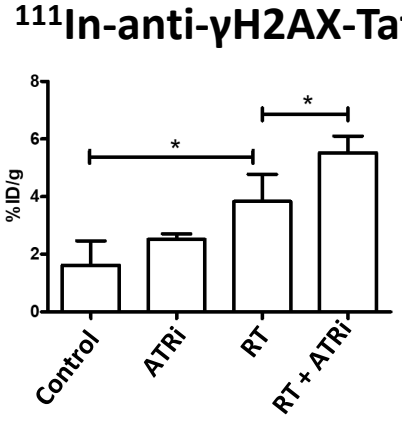


Cornelissen et al. Cancer Res 2011

Radiosensitisation

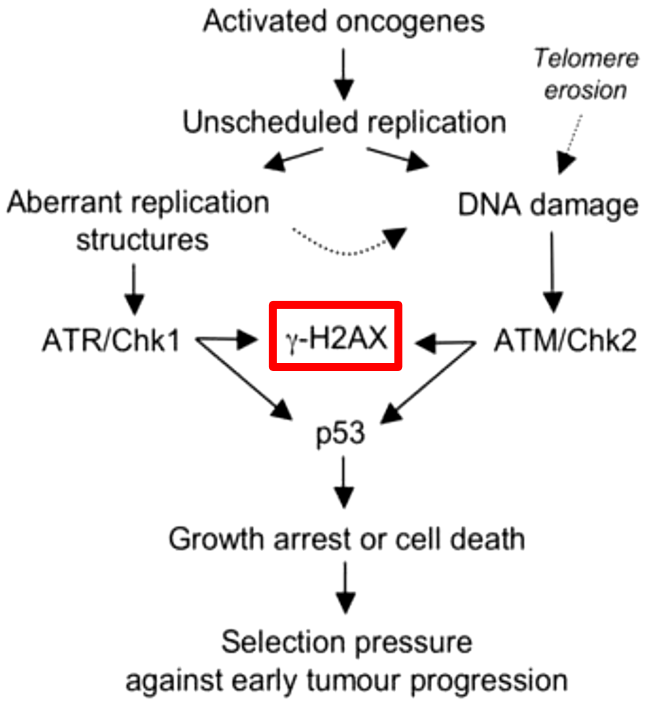


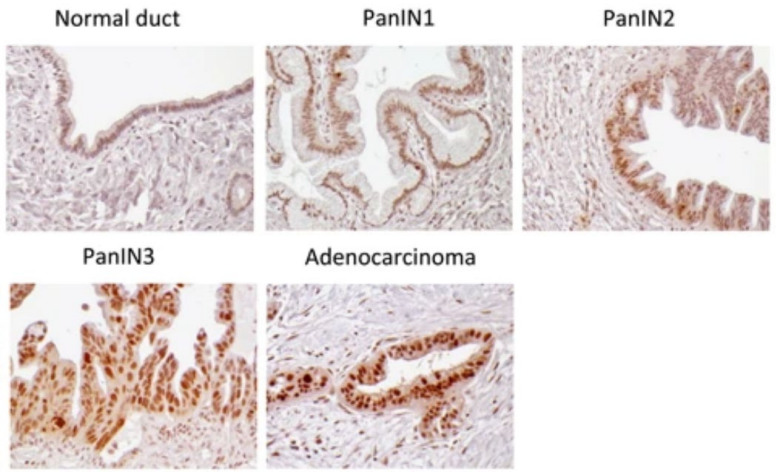


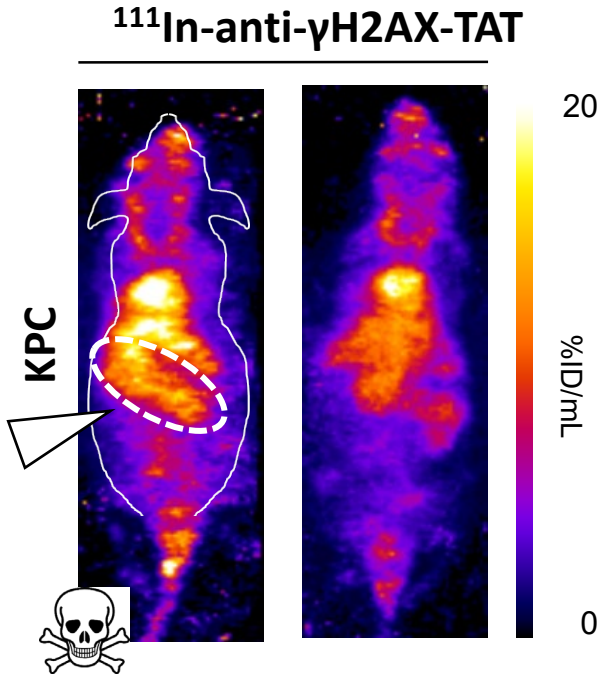


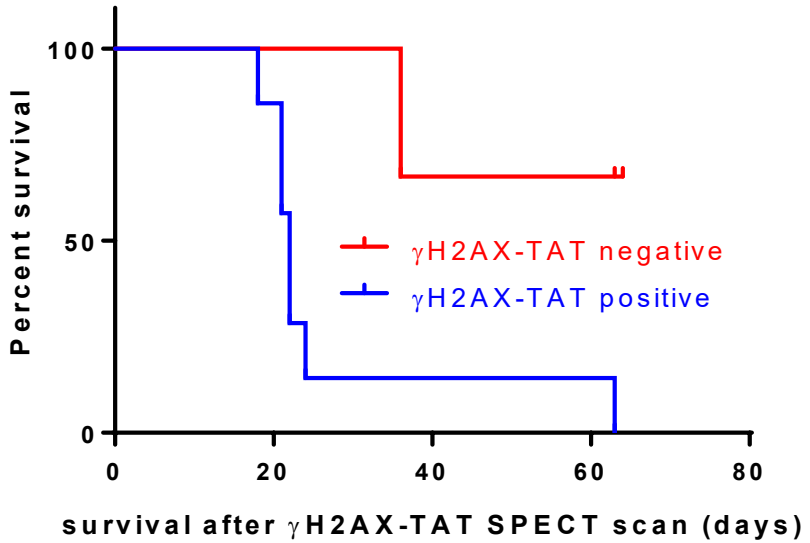
Fokas et al. CDD, 2012

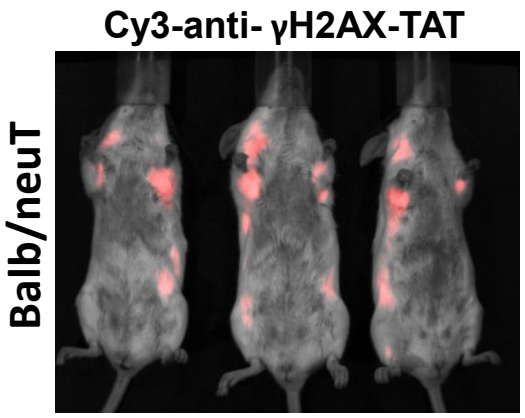
Early detection: hyperactivation of DDR







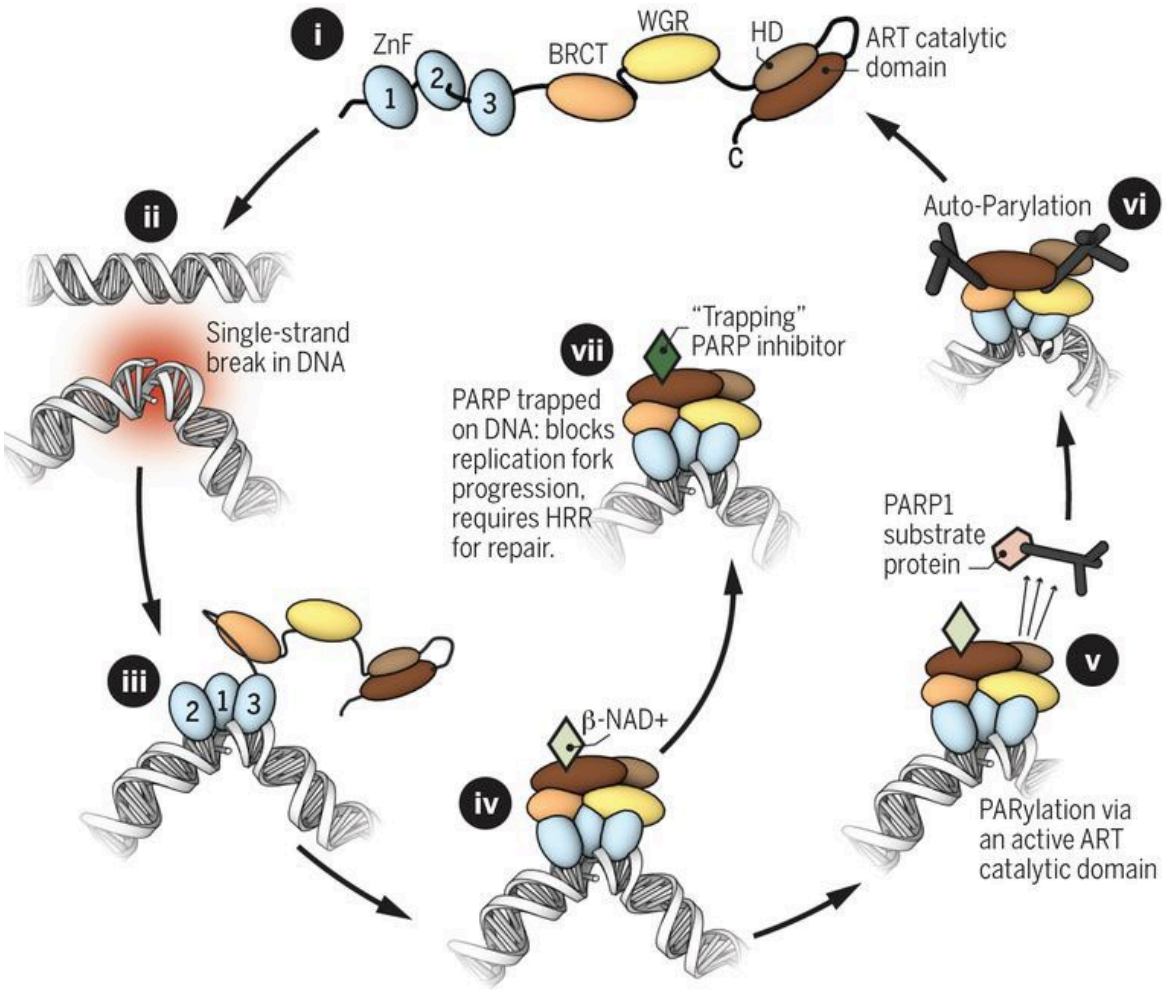


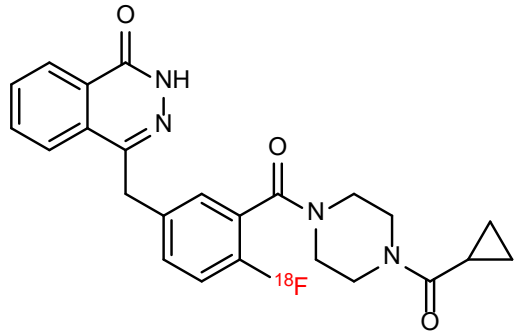


But not FDG ….

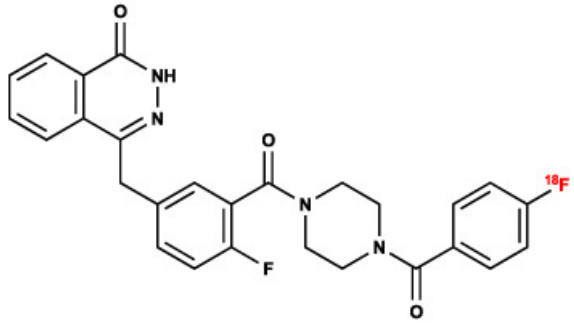
Knight et al. J Nucl Med 2020
Cornelissen Eur J Nucl Med Mol Imaging 2015

Targeting PARP

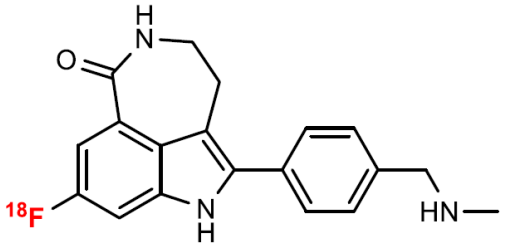




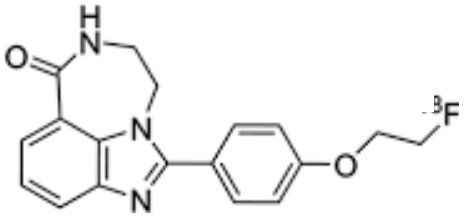
[^{18}F]olaparib



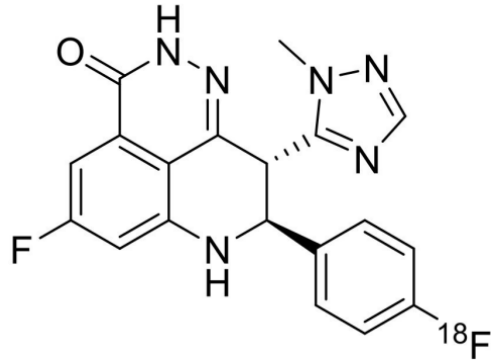
[^{18}F]PARPi



[^{18}F]rucaparib



[^{18}F]FTT



[^{18}F]talazoparib

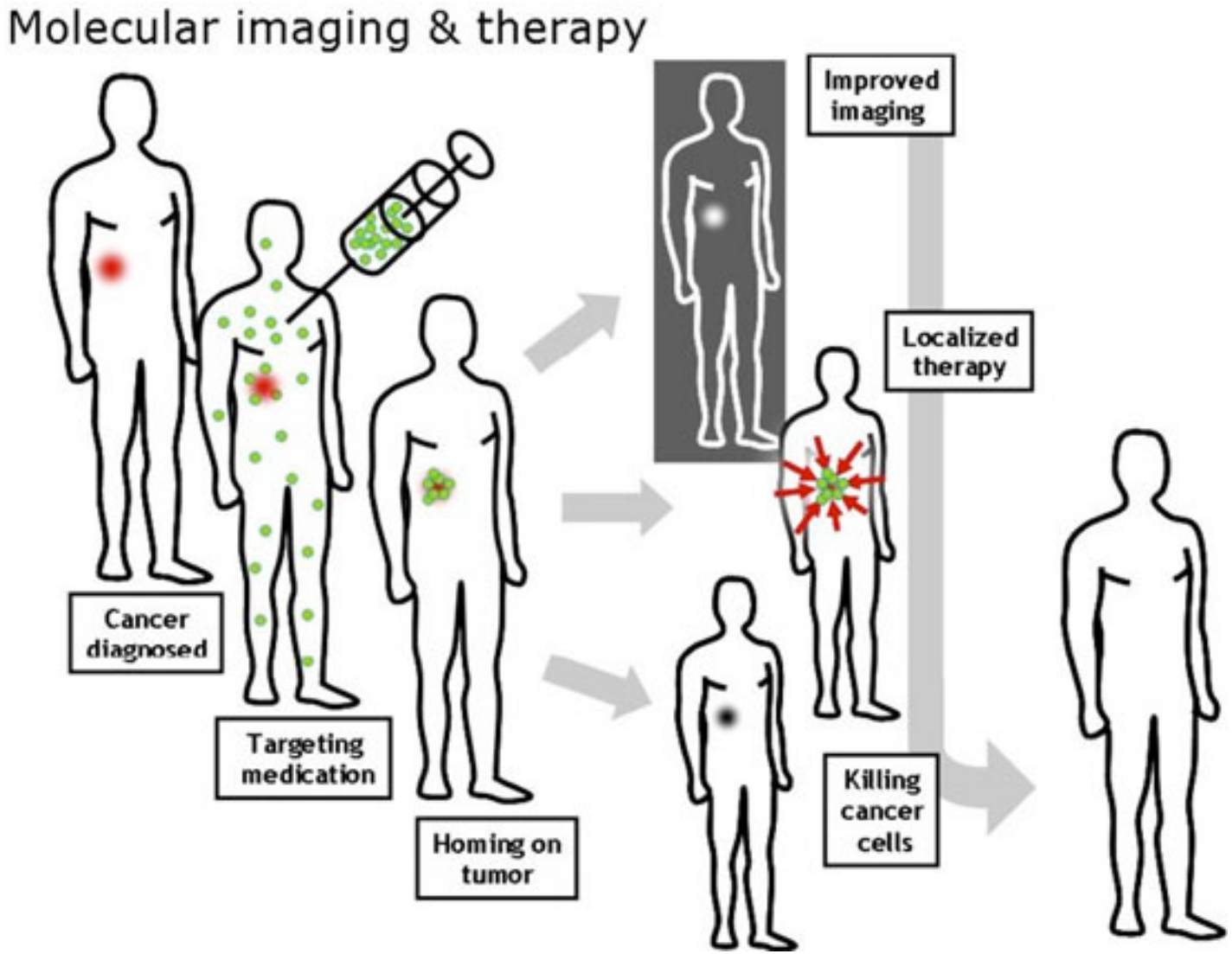
Chen et al. Clin Cancer Res 2021

Radiochemistry radiation protection



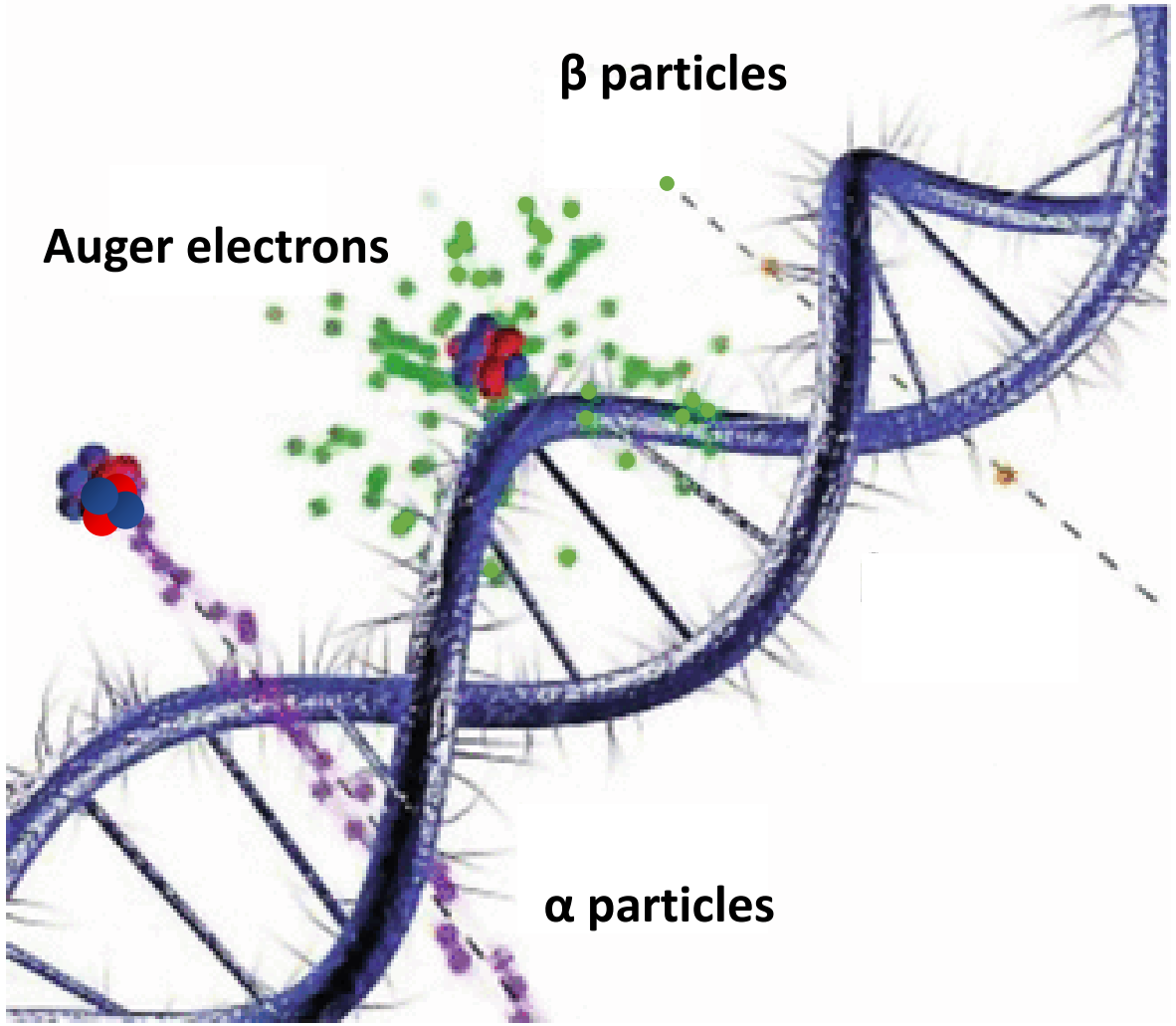


Nucleaire Geneeskunde, Moleculaire geneeskunde



Radionucliden therapie

Inside-out principle



β : ^{131}I, ^{90}Y, ^{177}Lu

α : ^{225}Ac, ^{223}Ra, ^{211}At, ^{212}Pb, ^{213}Bi

AE: ^{125}I, ^{123}I, ^{111}In

Radionucliden therapie

1940s Saul Hertz

1st ^{131}I therapy, Thyroid CA*

1980s,

SSRT, ^{111}In, NETs

^{131}I-MIBG, neuroblastoma

Early 1990s, first matched pair ^{90}Y/^{86}Y

SIRT, liver

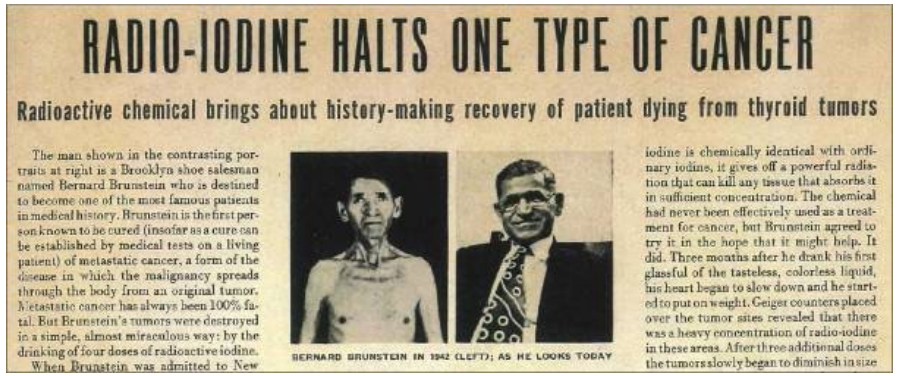
2000s, RIT, haematological cancers

^{111}In/^{90}Y pair

2013, 223Ra, 1st alfa emitter approval

^{177}Lu-DOTATATE FDA approved

Recently, PSMA, FAPI, integrins, GRP ….



RADIO-IODINE HALTS ONE TYPE OF CANCER

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors

The man shown in the contrasting portraits at right is a Brooklyn shoe salesman named Bernard Brunstein who is destined to become one of the most famous patients in medical history. Brunstein is the first person known to be cured (insofar as a cure can be established by medical tests on a living patient) of metastatic cancer, a form of the disease in which the malignancy spreads through the body from an original tumor. Metastatic cancer has always been 100% fatal. But Brunstein's tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine.

When Brunstein was admitted to New

BERNARD BRUNSTEIN IN 1942 (LEFT); AS HE LOOKS TODAY

iodine is chemically identical with ordinary iodine, it gives off a powerful radiation that can kill any tissue that absorbs it in sufficient concentration. The chemical had never been effectively used as a treatment for cancer, but Brunstein agreed to try it in the hope that it might help. It did. Three months after he drank his first glassful of the tasteless, colorless liquid, his heart began to slow down and he started to put on weight. Geiger counters placed over the tumor sites revealed that there was a heavy concentration of radio-iodine in these areas. After three additional doses the tumors slowly began to diminish in size

Feijtel et al. Curr Med Chem 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

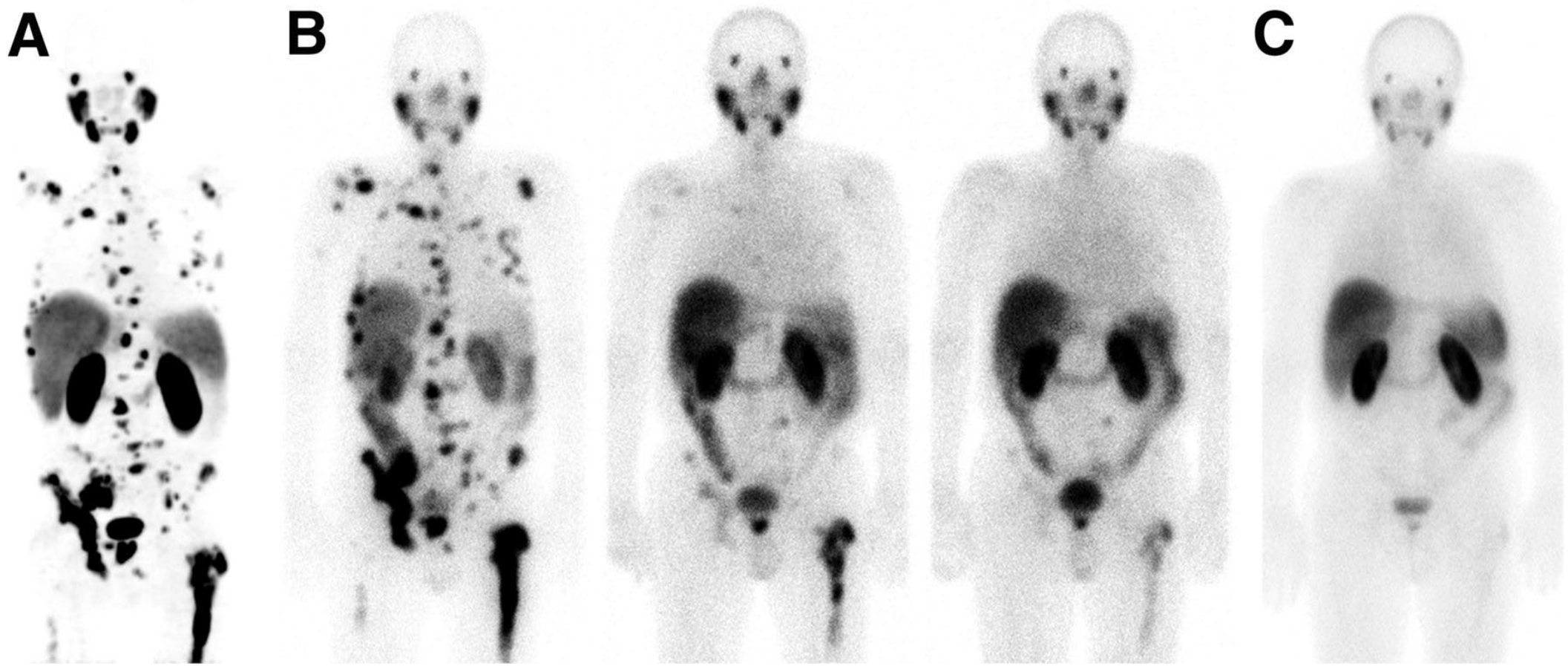
Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum,

MRT, PRRT, RNT, RLT, ….

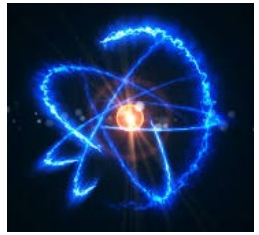
^{177}Lu-DOTATATE

^{177}Lu-PSMA

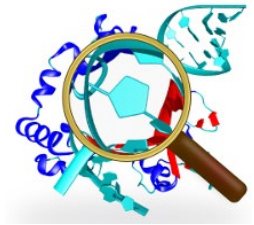


Echt?

(Nee, niet echt.)



Physics and dosimetry



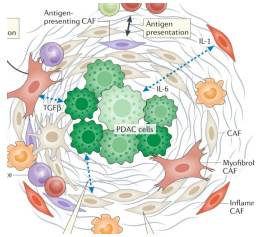
Biomarkers



Target distribution



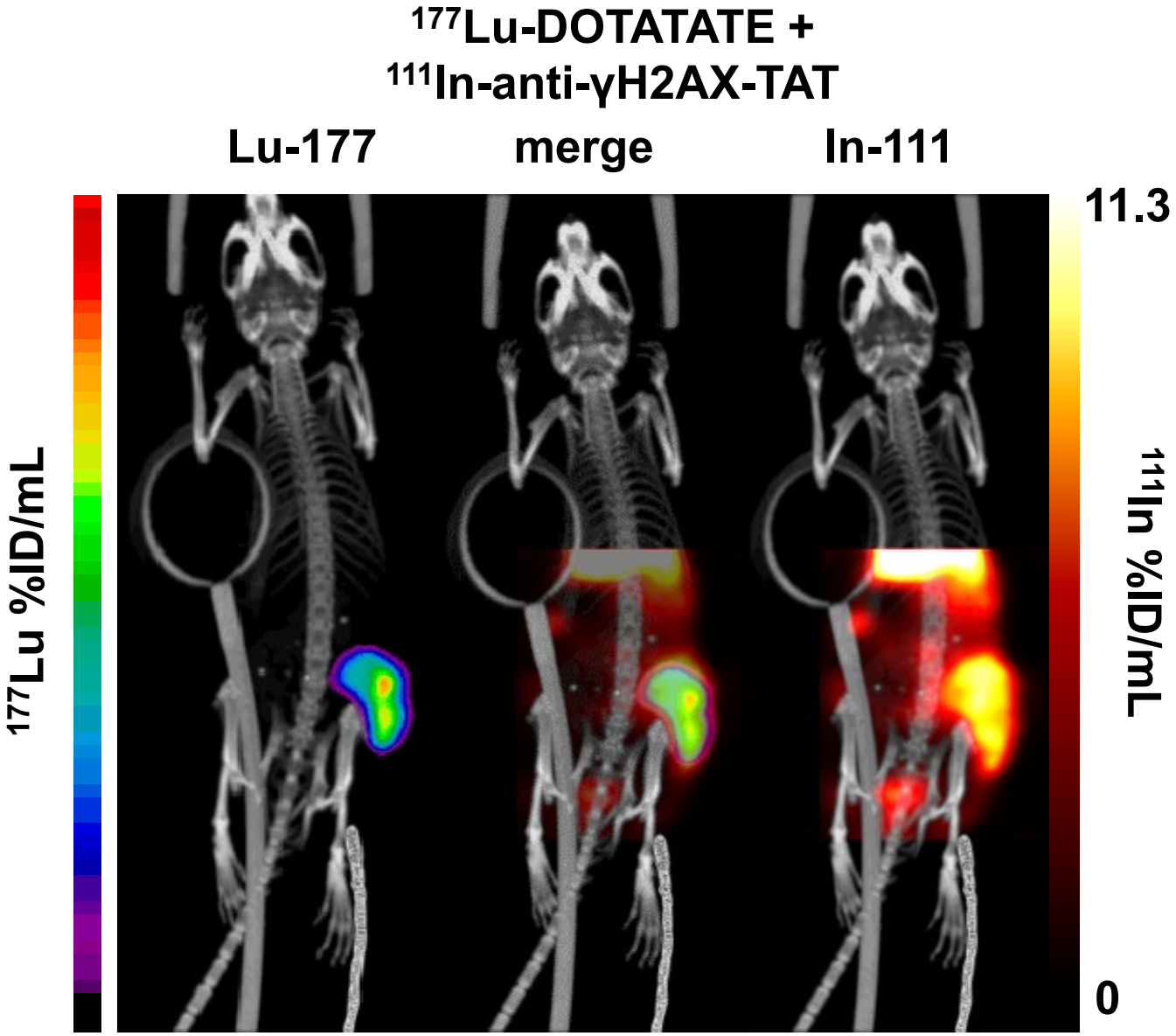
Combinations

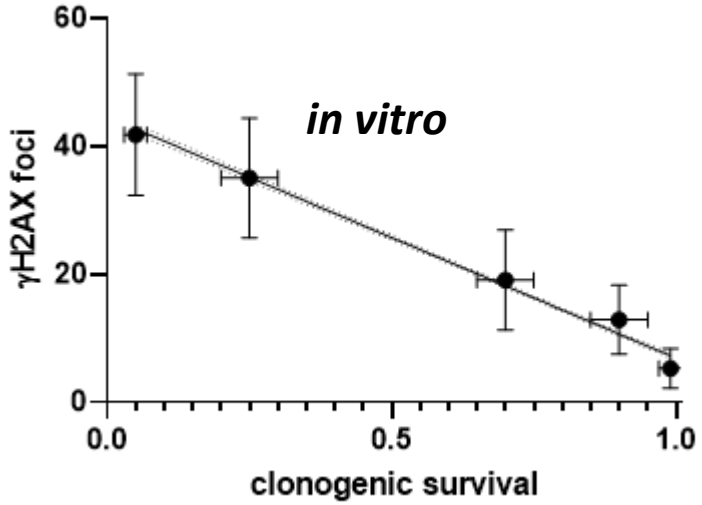


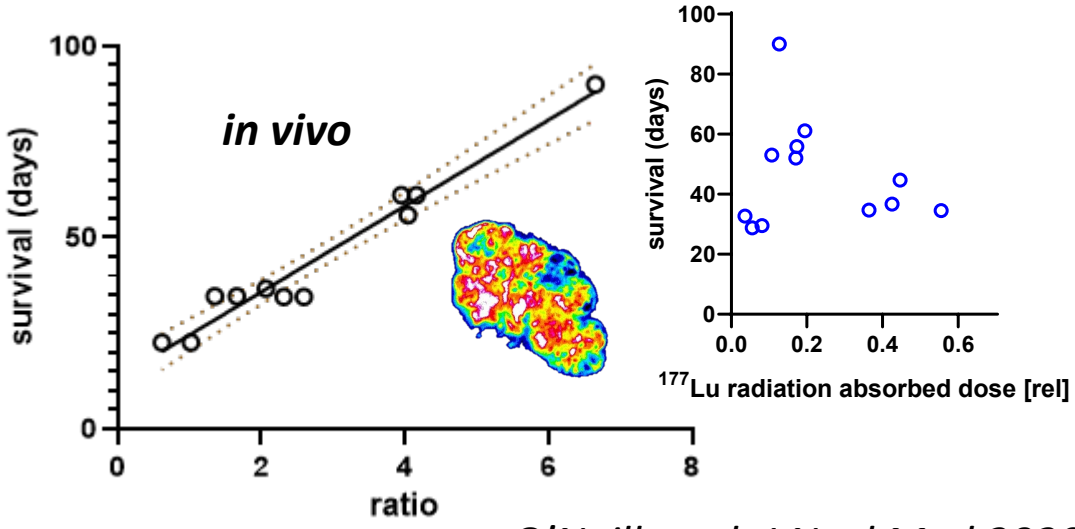
Microenvironment

BIOLOGY !

Biodosimetry after MRT: ^{177}Lu-DOTATATE





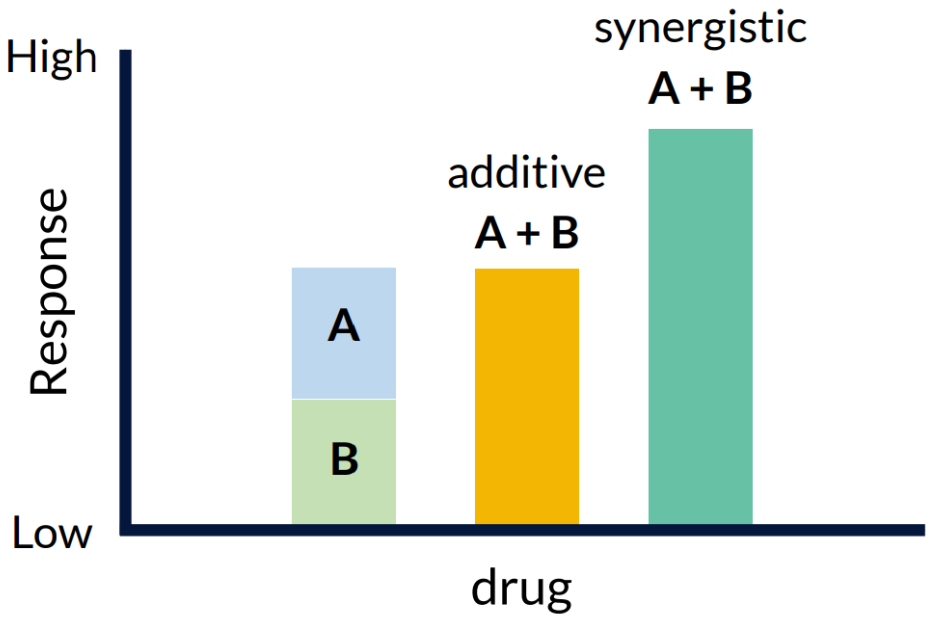


O'Neill et al. J Nucl Med 2020

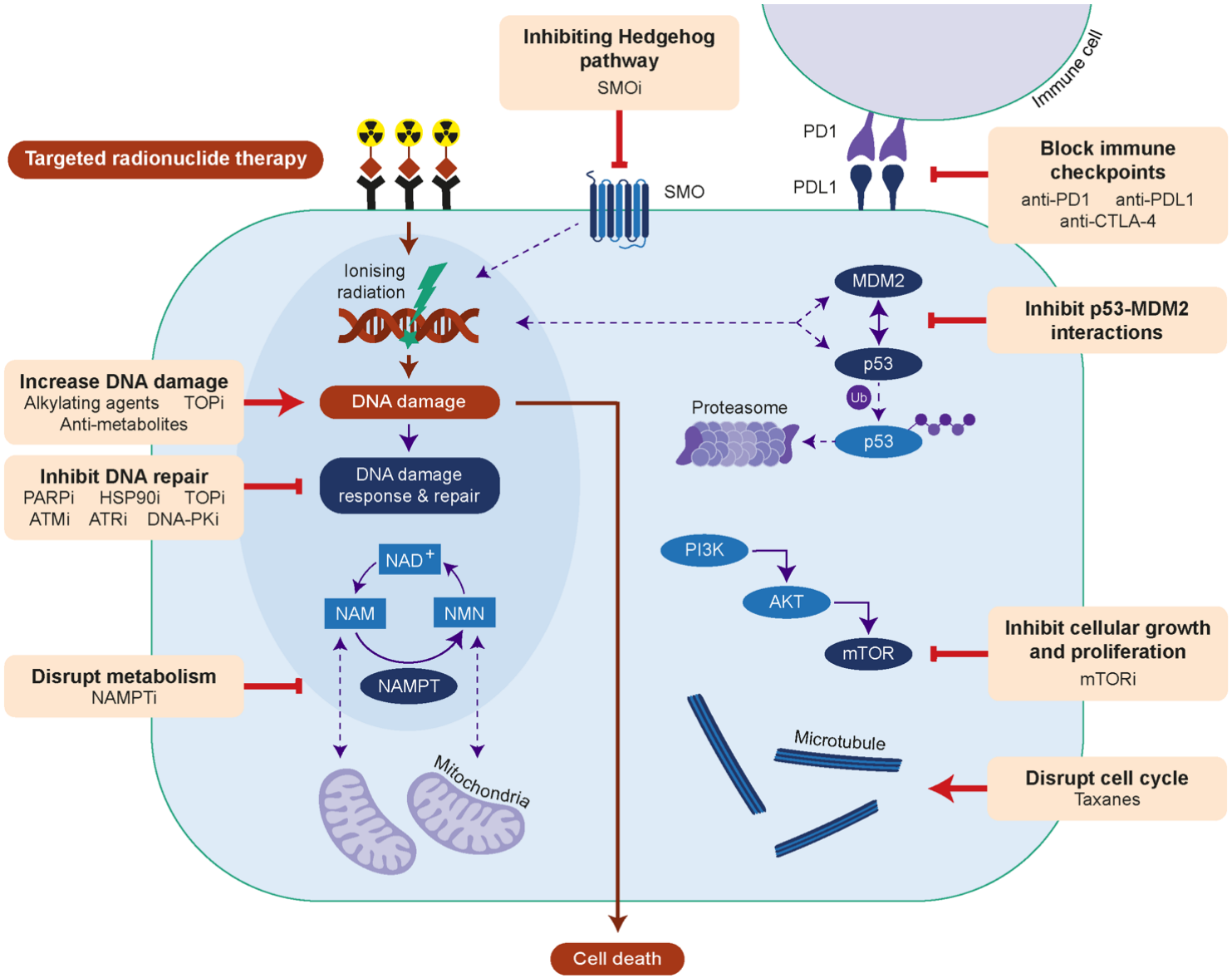
Poty et al. Theragnostics 2020: ^{225}Ac-pretargeted therapy

Terry et al. EJNMMI 2019

Combinaties

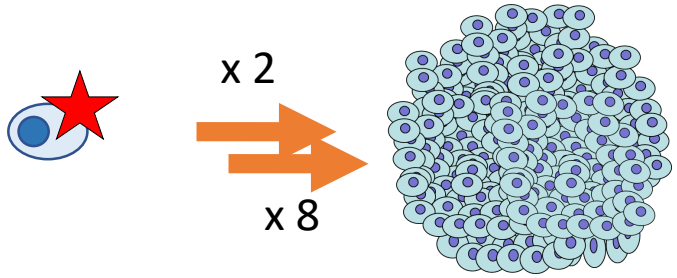


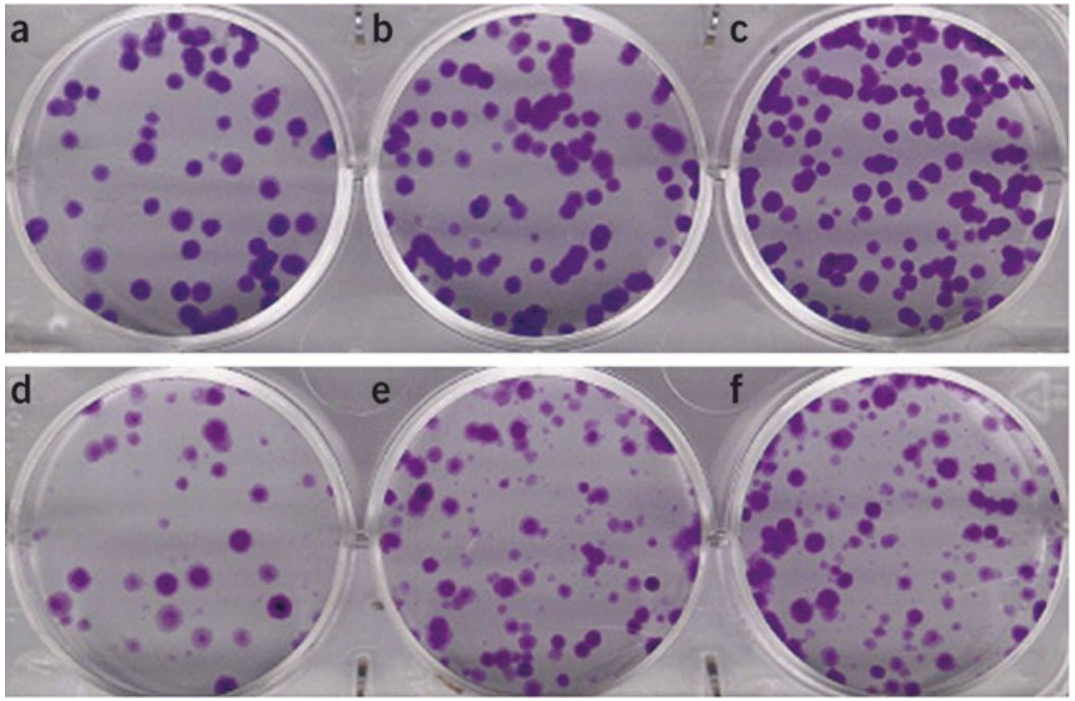
(11 clinical trials ongoing)

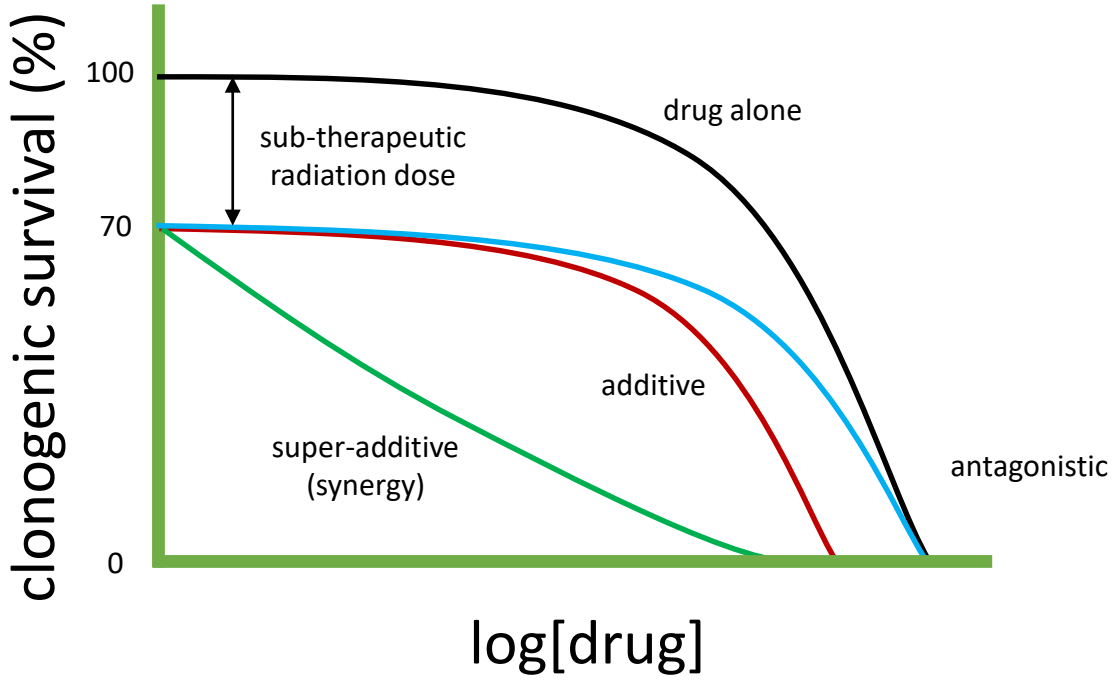


Combination therapy?

- Screen: clonogenic survival assay

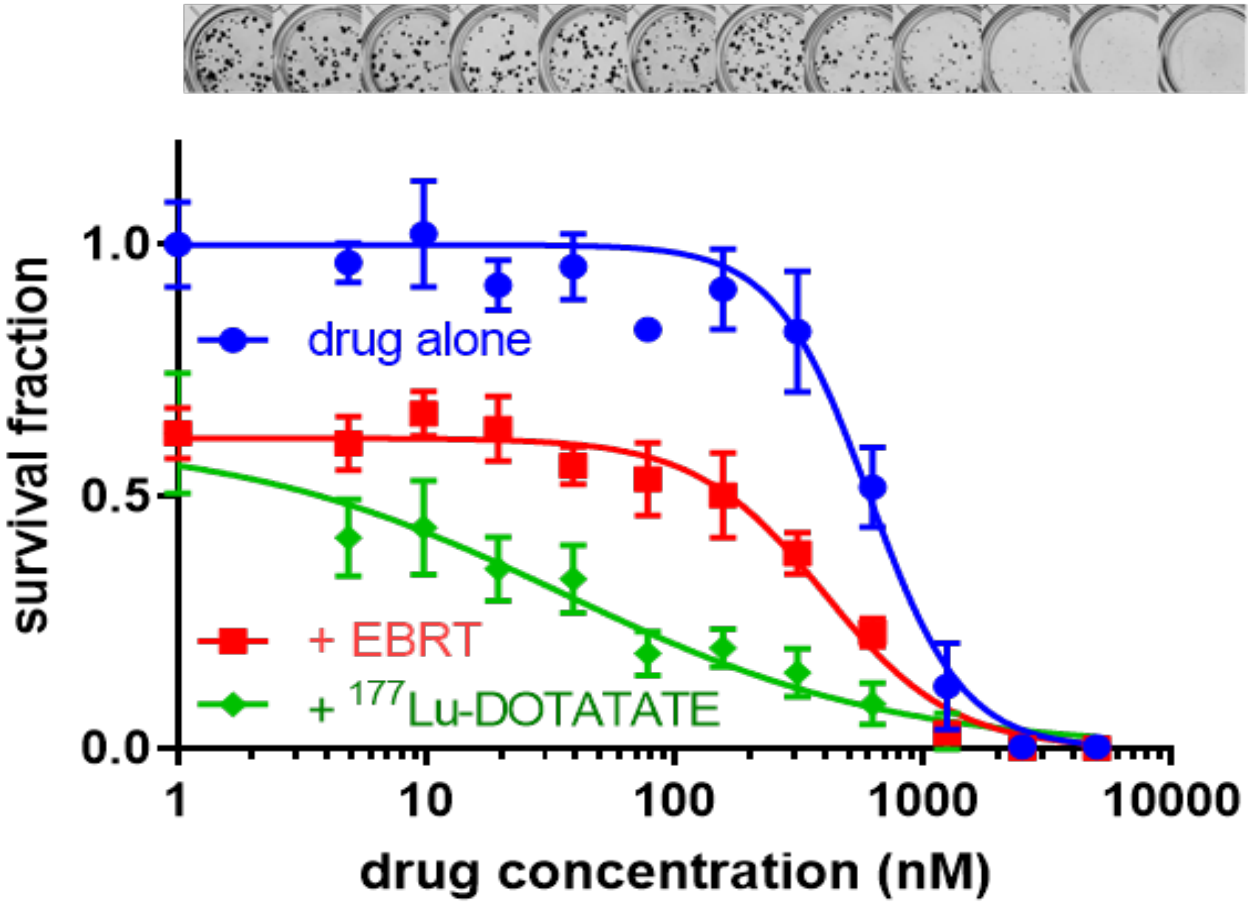






High throughput (96-well)

Combination screen (NET cell line): clonogenic!



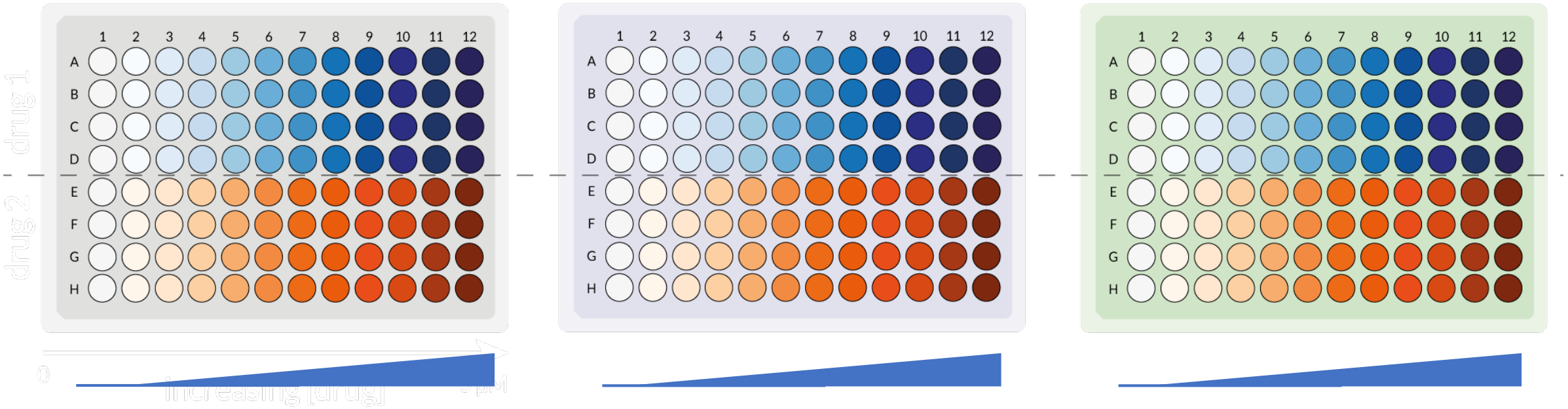
screen setup:

Extended screening

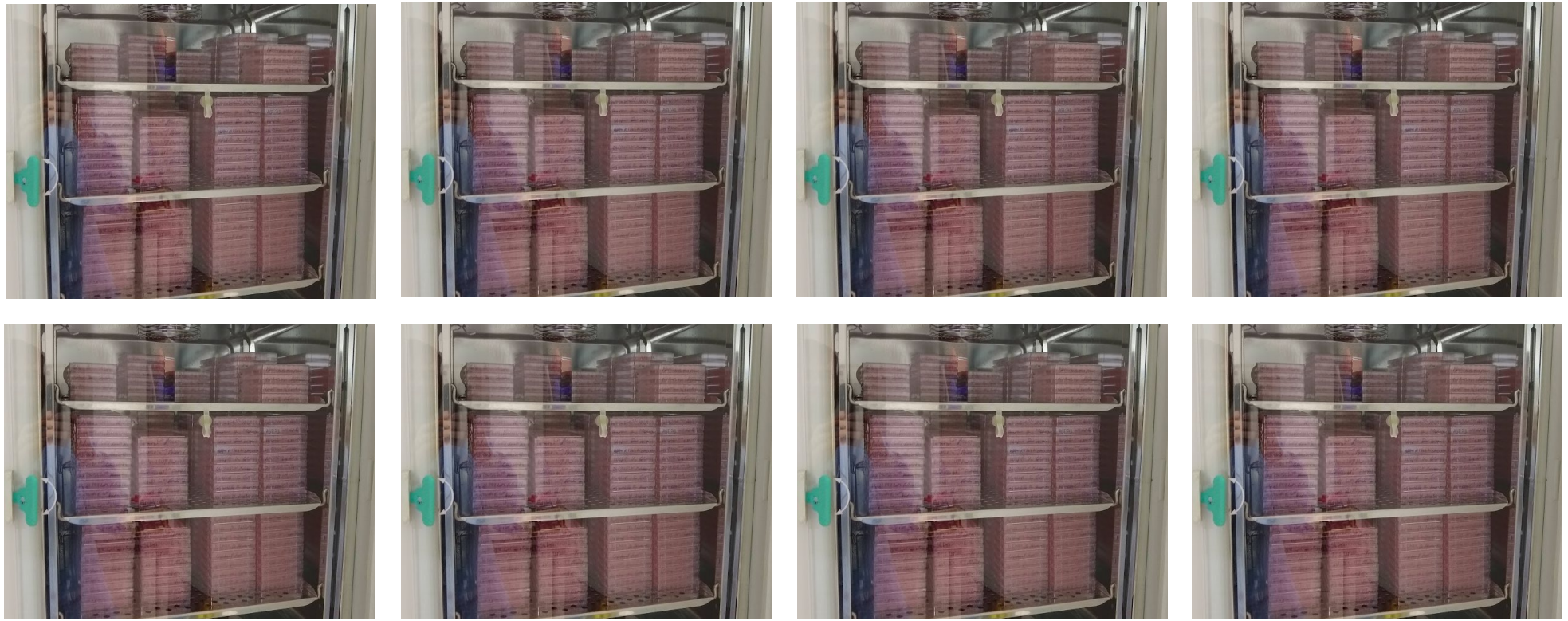
drug only

drug + ^{177}Lu-PSMA;
drug + ^{177}Lu-DOTATATE

drug + IR

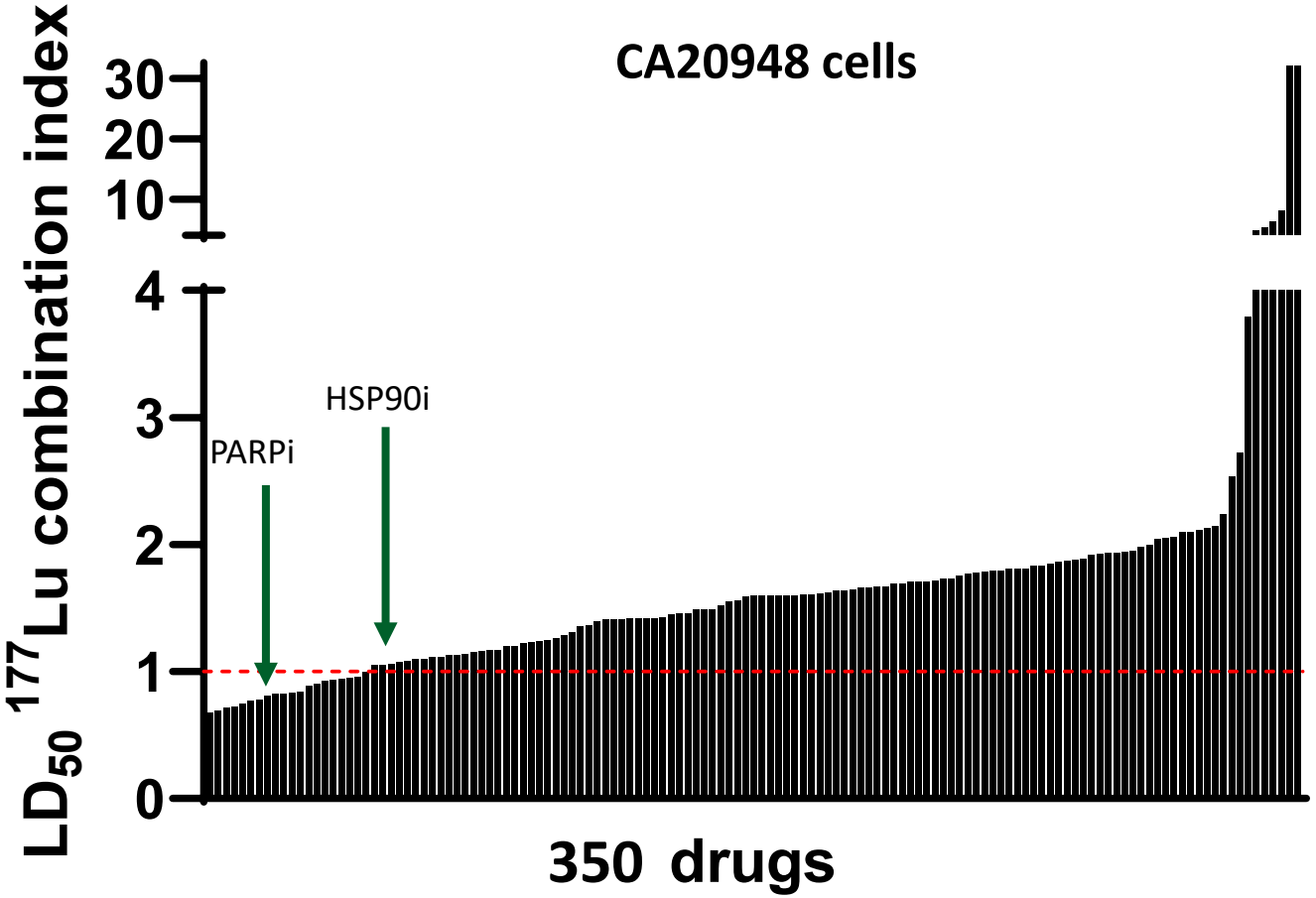


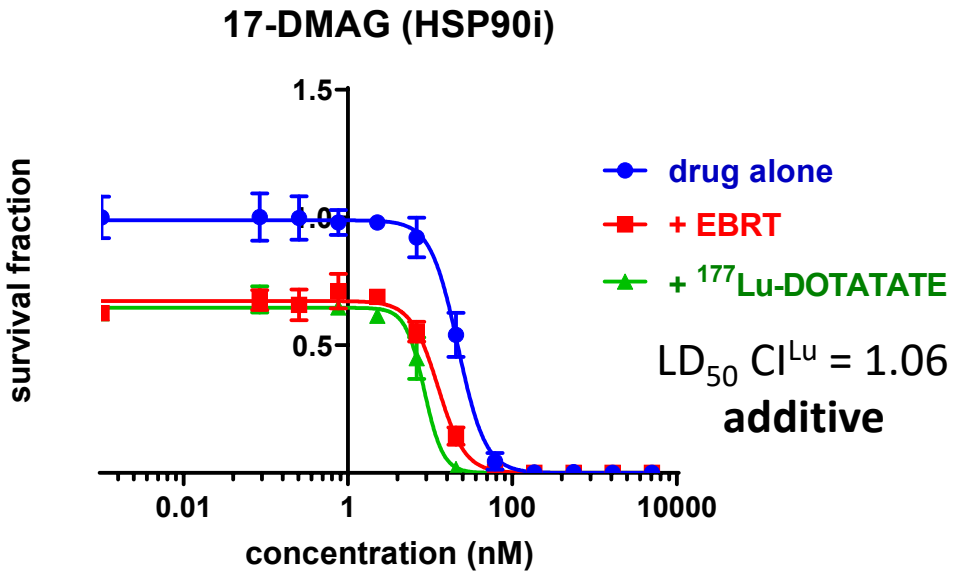
Even later…

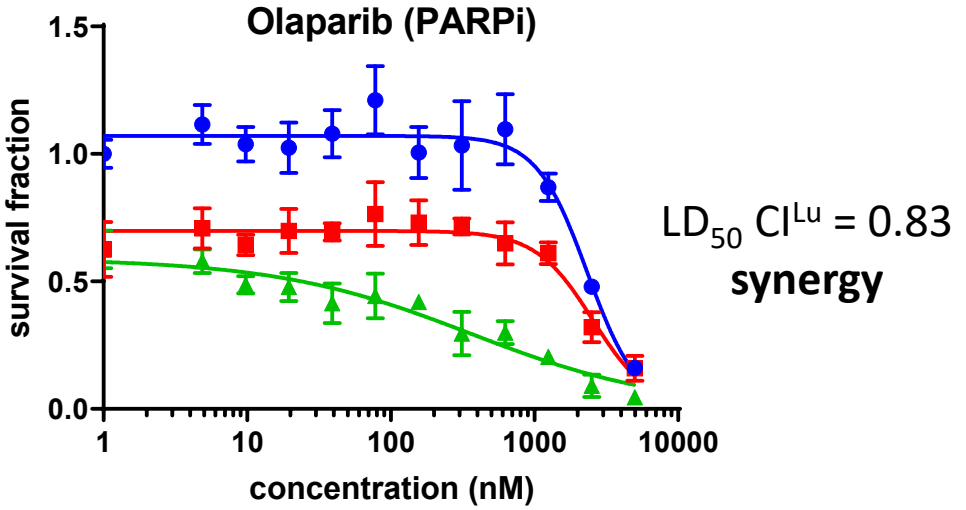


+ automatie

^{177}Lu-DOTATATE combination







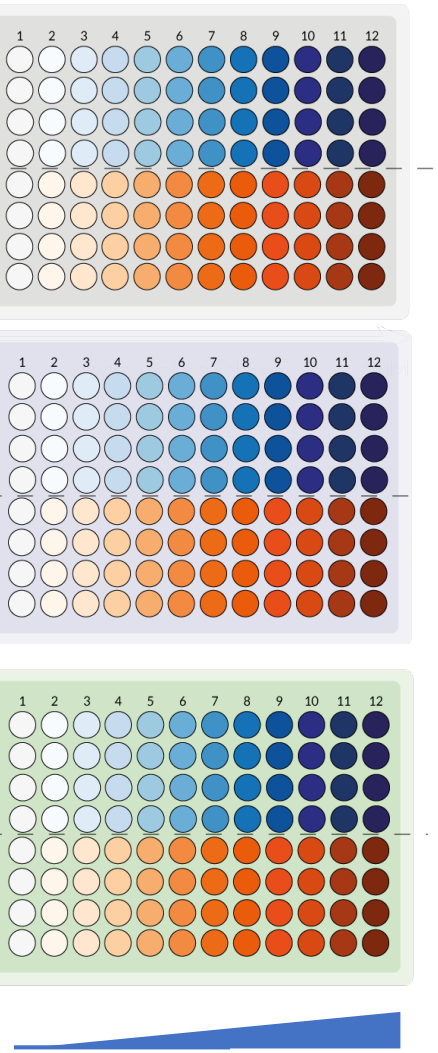
Combination therapy: ^{177}Lu-PSMA + drug

n = 1960 *22rv1*

drug only

drug + ^{177}Lu-PSMA

drug + IR



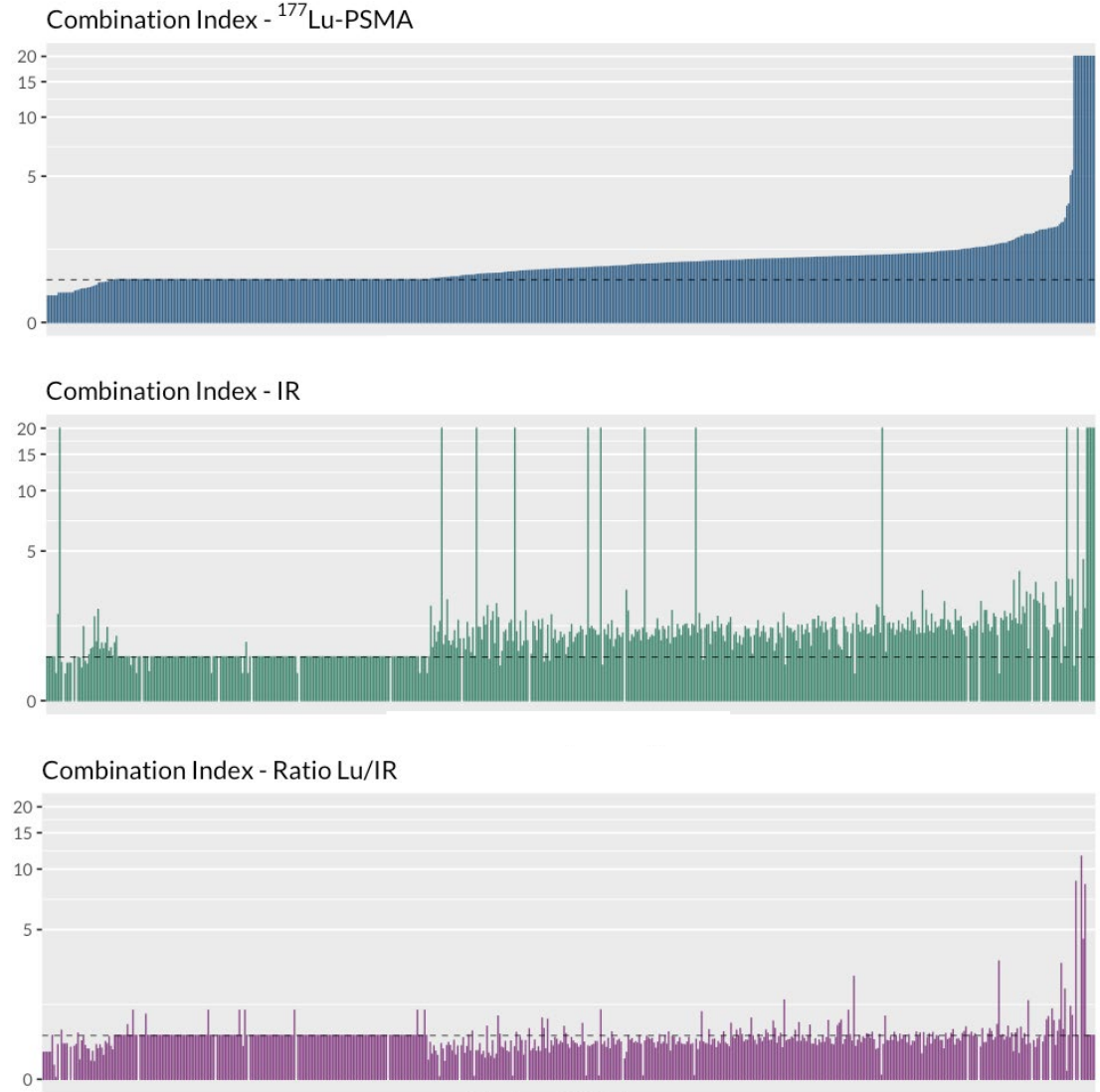
^{177}Lu-PSMA

External Beam Radiation

Ratio ^{177}Lu-PSMA / EBRT

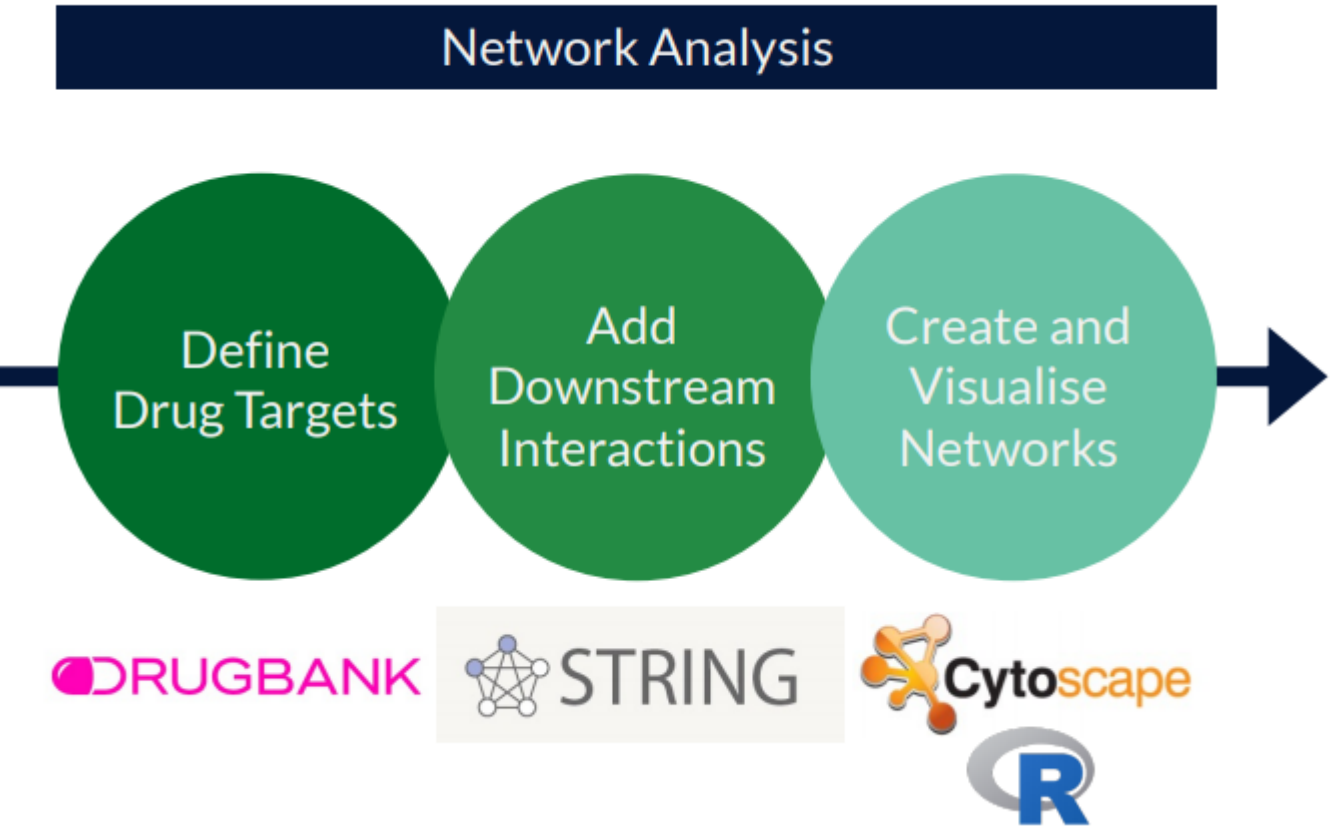
combination index

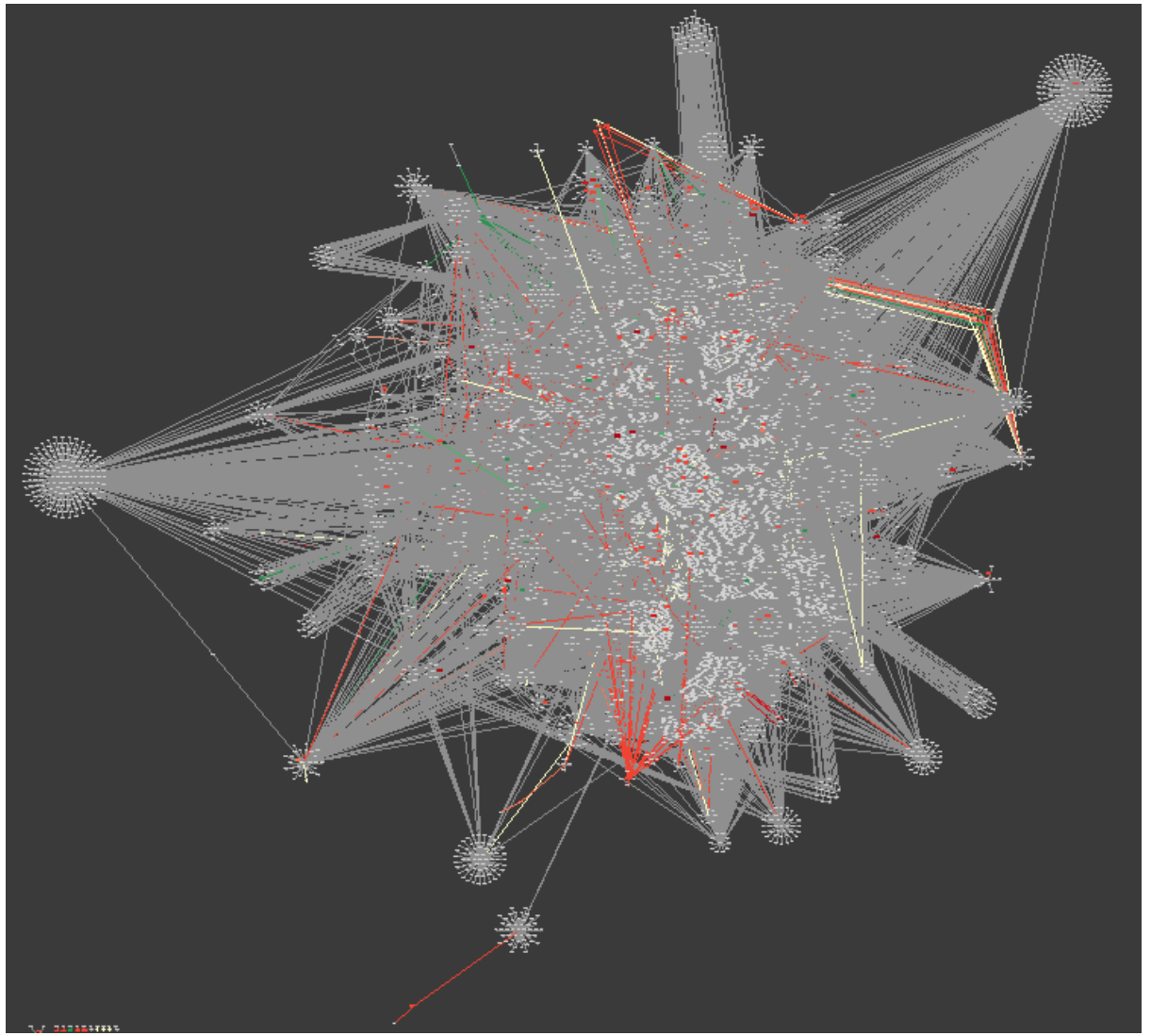
ratio



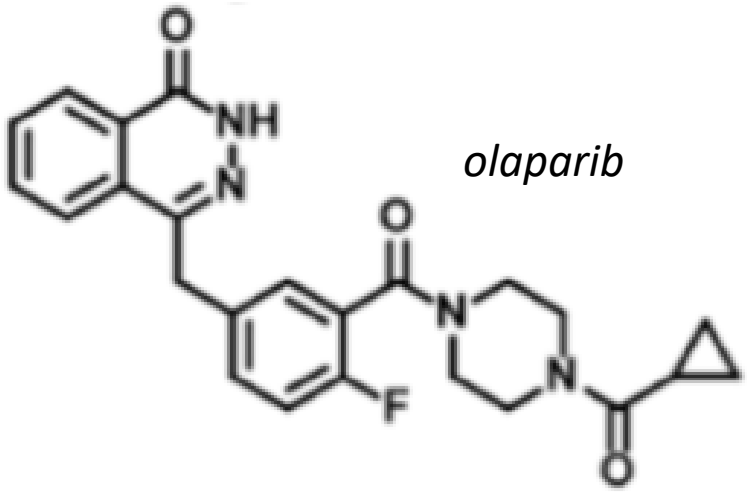
hits from 2,000 drugs

Combination therapy: ^{177}Lu-PSMA + drug

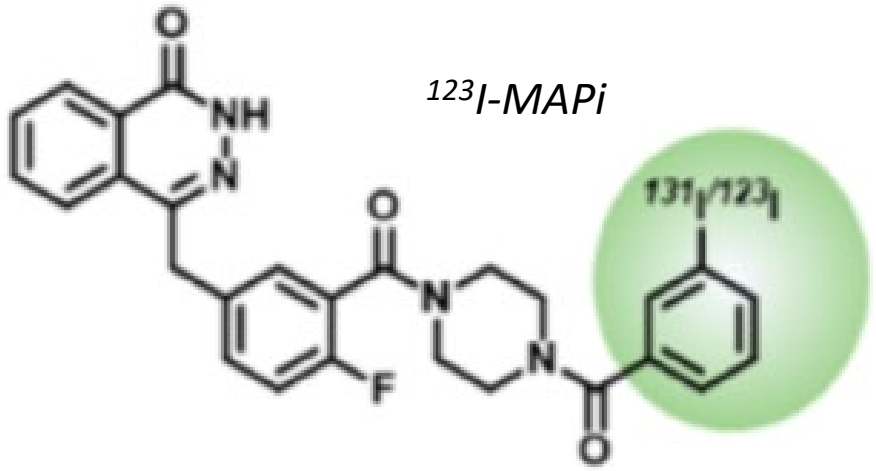




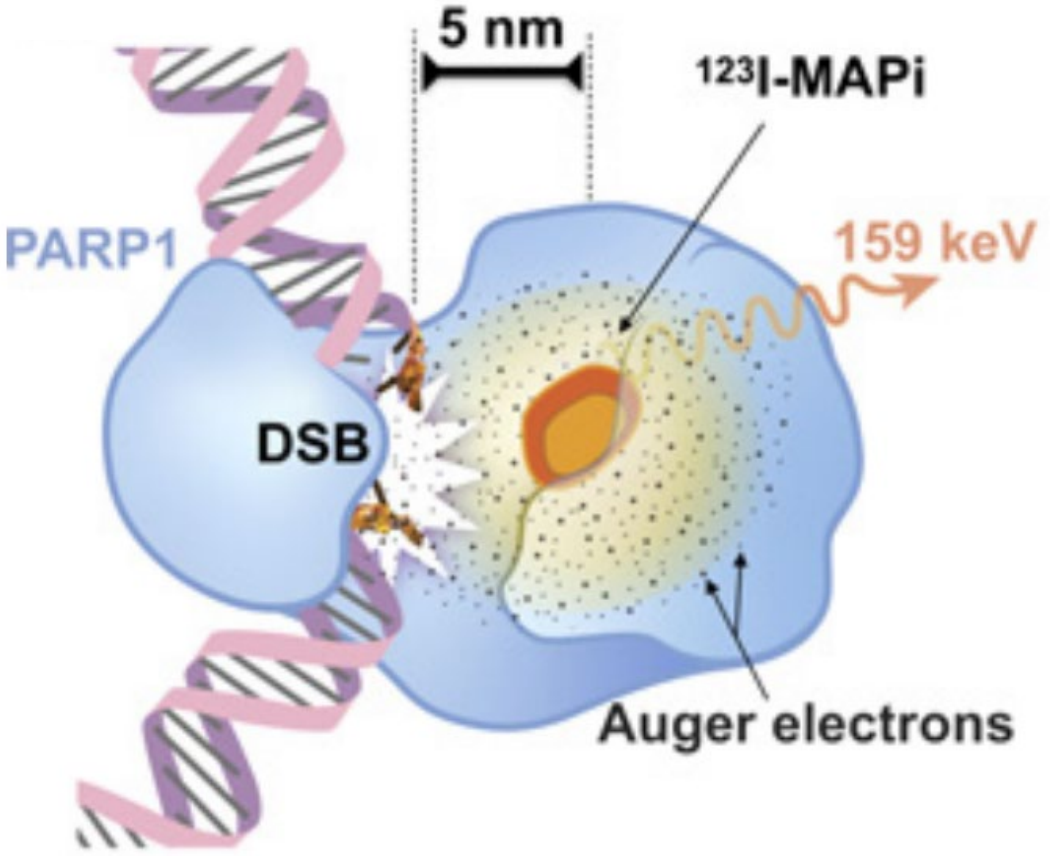
Auger electron therapy



olaparib



^{123}I-MAPi



UK vs. NL

UK

- User training 4 h
- RPS training minimal (1 day)
- Local training + retraining
- ‘Gold standard’ meetings: 2x / year
- University (3000 users): local RPS + departmental SRPS
- Responsibility for users
- RPS: only facilitating
- HoD responsible
  - Only appoint people with pre-existing knowledge



Acknowledgements

BC Lab past and present

Michael Mosley
Julia Baguña-Torres
Deborah Sneddon
Gemma Dias
Anna Pacelli
Mathew Veal
Kathy Chan
James Knight
Sofia Koustoulidou
Abirami Lakshminarayanan
Doreen Lau
Arvieri Putra
Sam Higgins
Florian Guibbal
Ed O'Neill
Javier Ajenjo
Hudson Alakonya
Claudia Fraser
Tiffany Chan
Mary-Ann Xavier
Cristina Marculescu
Joshua Bugajski
Gianluca Destro
Christine Habjan





Imcore **Veerle Kersemans**, Katherine Vallis, Becky Hueting, Sean Smart, Sheena Wallington
Veronique Gouverneur, Thomas Wilson, Ben Davis, Zijun Chen
Julie Nonnekens, Marion de Jong, Mark Konijnenberg (Erasmus MC)
Steve Leppla, Shui Liu (NIH)
Kate Vallis, Tim Humphrey, Andy Ryan, Thomas Brunner, Manos Fokas (MRC Oxford Institute)

