Universitätsklinikum Würzburg

Institut für Radiobiologie der Bundeswehr

The relationship between absorbed dose and DNA damage in lymphocytes after radionuclide therapy

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ICTR-PHE 2016

Klinik und Poliklinik für Nuklearmedizin
Direktor: Prof. Dr. A. Buck

Motivation

- The use of ionizing irradiation can cause DNA double strand breaks

- Aim of internal dosimetry in radionuclide therapy
  - Define absorbed doses in critical organs and tumors

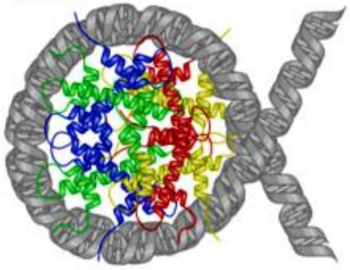
- For a better assessment of radiation damage:

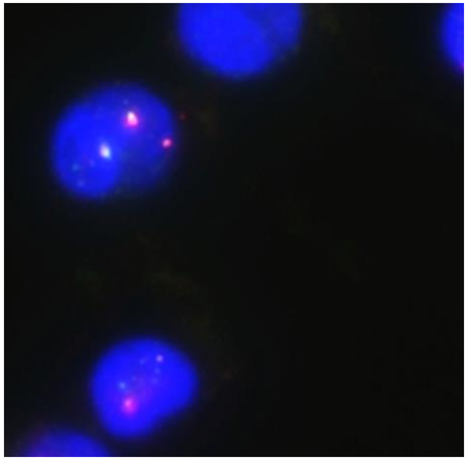
  - **Combination of internal dosimetry and biodosimetry (direct way to determine DNA damage)**

  - Describe the time course of DNA damage biomarkers in blood lymphocytes after radionuclide therapy

Biomarkers for DSBs: γ-H2AX and 53BP1

- 146 base-pairs of the DNA are wrapped around histone octamer
- DSB formation results in phosphorylation of the protein “histone H2AX”
  - **γ-H2AX**
- Accumulation of the damage sensor **53BP1** in the vicinity of the DSB
- Visualization
  - Immunofluorescence staining of lymphocytes
  - Microscopically visible foci
  - Manual counting of co-localized γ-H2AX and 53BP1 foci





co-localized γ-H2AX and 53BP1 foci

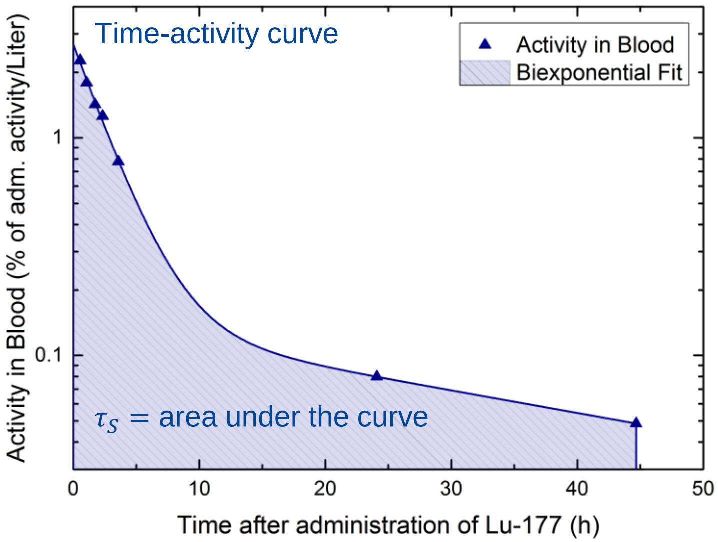
Usage of the DNA-Damage Assay

- Quantitative proof of radiation
  - 1 focus ≙ 1 DSB
  - Linearity between the number of radiation induced foci (RIF) and the absorbed dose only shown after external irradiation

- Only few data after internal exposure e.g. Nuclear Medicine are available
  - Continuous irradiation with decreasing dose rate

Blood based dosimetry for ^{177}Lu and ^{131}I *

- Blood as source organ (self-irradiation)
  - β-radiation originating from activity in the blood is fully deposited
- Whole body as a source organ
  - only γ-irradiation was taken into account
- Absorbed dose to blood: $\boldsymbol{D_{Bl} = A_0 \cdot \left(S_{Bl\leftarrow Bl} \cdot \tau_{per\ ml\ Bl} + \frac{s_{WB\leftarrow\gamma\ WB}}{weight^{2/3}} \cdot \tau_{WB}\right)}$



- $S_{T\leftarrow S}$: mean absorbed dose per nuclear disintegration in the target organ
- τ: time integrated activity coefficient

Nuclide	$\boldsymbol{E_{max}}$ **(keVBq^{-1}s^{-1})**	$\boldsymbol{S_{Bl\leftarrow Bl}}$ **(GymlGBq^{-1}h^{-1})**	$\boldsymbol{s_{WB\leftarrow\gamma\ WB}}$ **(GyGBq^{-1}h^{-1})**
^{177}Lu	148	85.3	0.00185
^{131}I	187	108.0	0.01880

Results

- Motivation

- Basics
  - DNA damage
  - Calculation of absorbed dose to the blood

- Results
  - **In-vitro calibration**
  - In-vivo patient study: ^{177}Lu-therapy
  - In-vivo patient study : ^{131}I-therapy

- Summary

PLOS | ONE

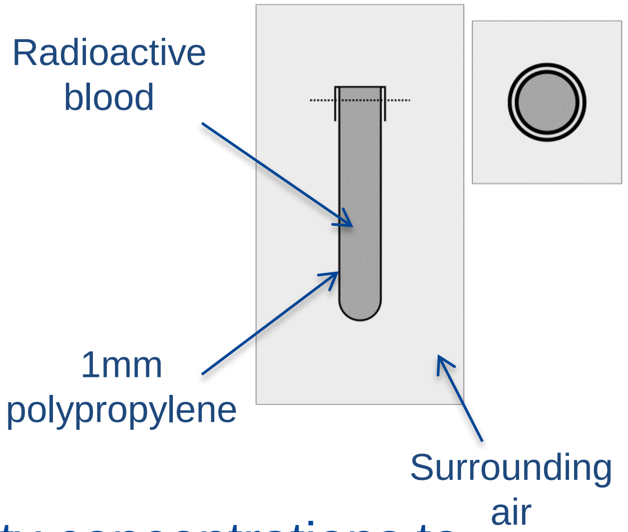
RESEARCH ARTICLE

Calibration of the γ-H2AX DNA Double Strand Break Focus Assay for Internal Radiation Exposure of Blood Lymphocytes

Uta Eberlein[1]*, Michel Peper[2], Maria Fernández[1], Michael Lassmann[1‡], Harry Scherthan[2‡]

Calculation of absorbed dose to blood after in-vitro irradiation

- Absorbed dose rates per nuclear disintegrations occurring in 1 ml of blood
  - Monte Carlo simulation for photons and electrons
  - Radiation transport code: MCNPXv2.71

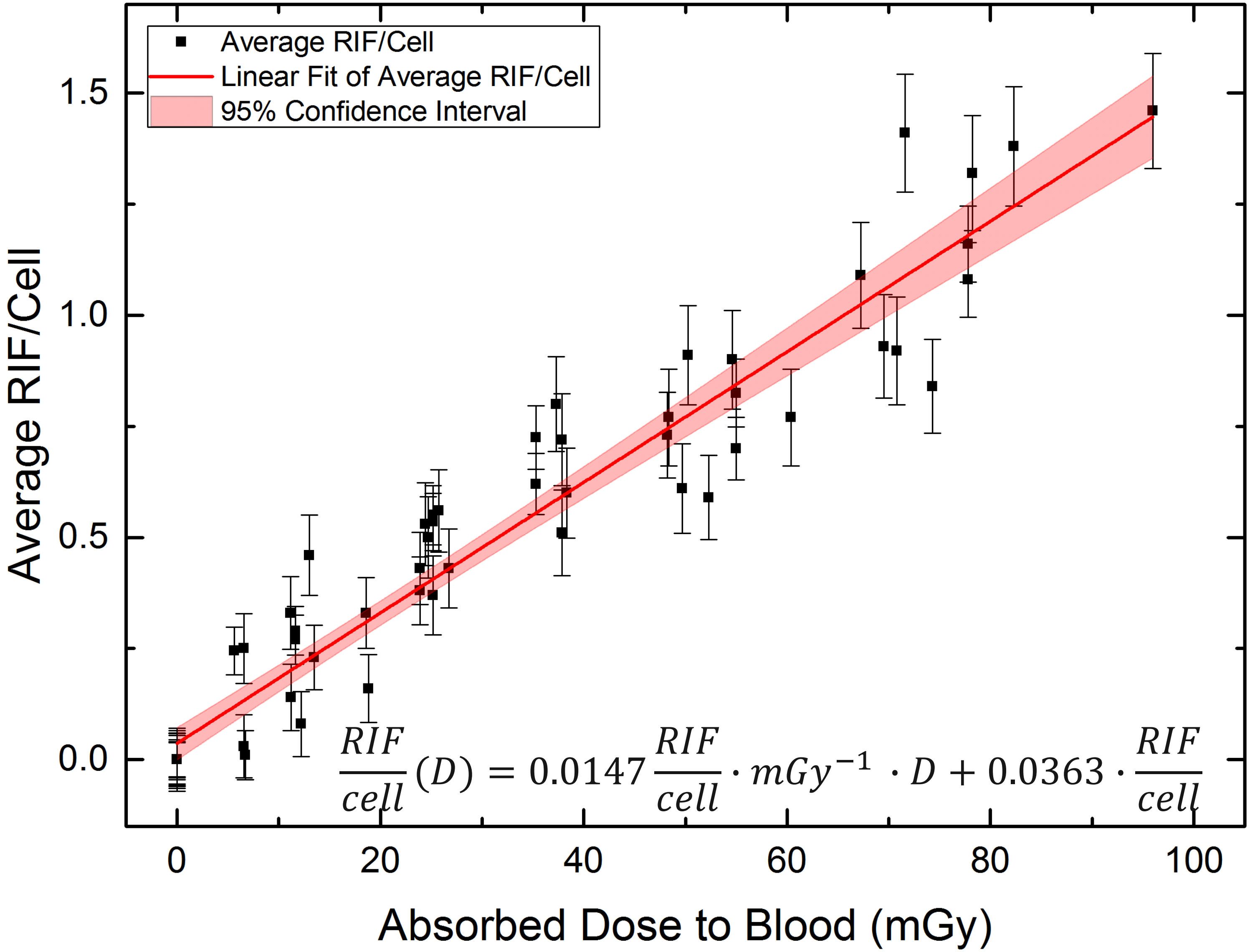


- Absorbed Dose (in 1ml) to the blood
  - ^{177}Lu: 83 mGy/MBq @ 1 h irradiation
  - ^{131}I: 110 mGy/MBq @ 1 h irradiation

- Prepare blood samples containing different activity concentrations to realize different absorbed doses to the blood: 6-95 mGy
  - 0.25 MBq – 4 MBq

- 3 healthy blood donors
- 9 experiments: 2 experiments with ^{131}I and 1 with ^{177}Lu

In-vitro calibration: RIF* as a function of absorbed dose to blood



$$\frac{RIF}{cell}(D) = 0.0147\,\frac{RIF}{cell}\cdot mGy^{-1}\cdot D + 0.0363\cdot\frac{RIF}{cell}$$

Results

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  - Calculation of absorbed dose to the blood
- Results
  - In-vitro calibration
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  - In-vivo patient study: ^{131}I-therapy
- Summary

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-015-3083-9

ORIGINAL ARTICLE

DNA damage in blood lymphocytes in patients after ^{177}Lu peptide receptor radionuclide therapy

Uta Eberlein[1] · Carina Nowak[2] · Christina Bluemel[1] · Andreas Konrad Buck[1] · Rudolf Alexander Werner[1] · Harry Scherthan[2] · Michael Lassmann[1]

Patients during peptide receptor radionuclide therapy (PRRT)

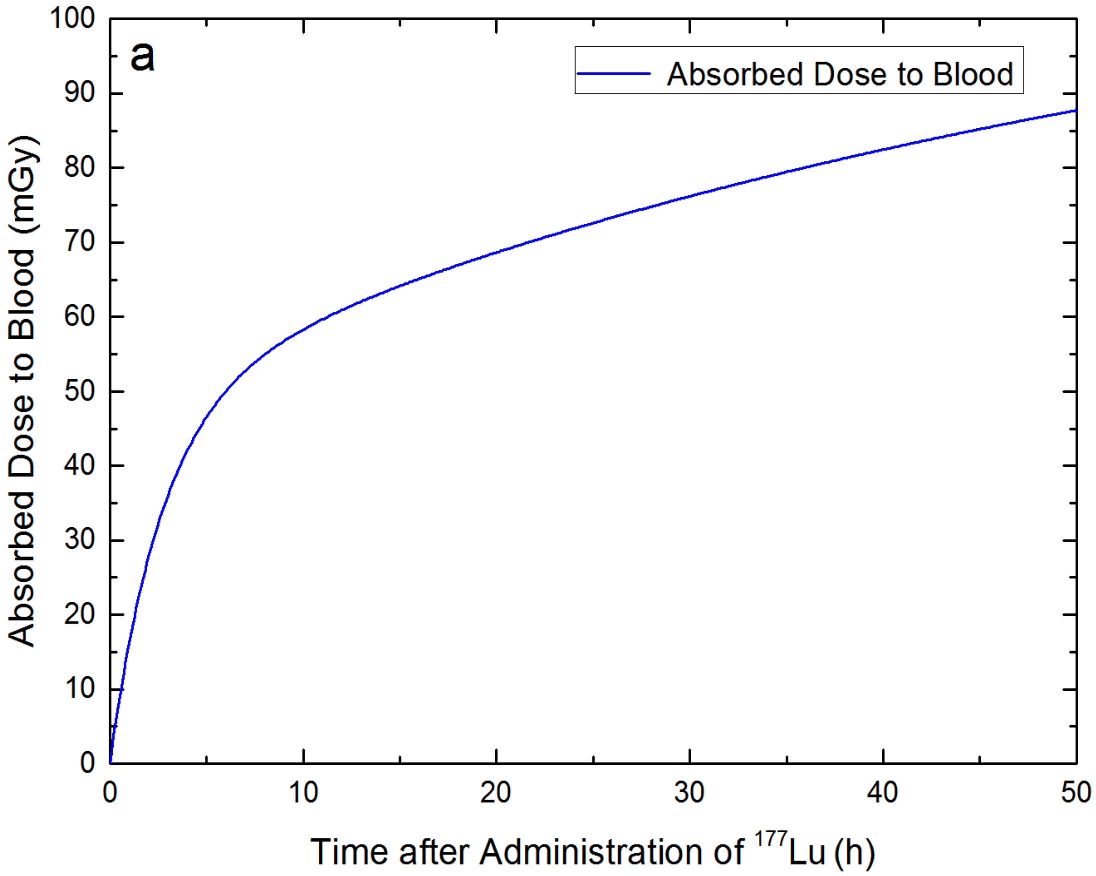
- ^{177}Lu-DOTA-TATE or DOTA-TOC for the treatment of tumors overexpressing somatostatin receptors (SSTR 2A)
  - Primarily: non-operable neuroendocrine tumors
  - Meningioma, thyroid cancer, or unknown primary

- 16 patients
  - 1st PRRT-therapy
  - Administered activity: (7.2 ± 0.4) GBq

- blood withdrawals
  - Background sample before therapy
  - 1h, 2h, 3h, 4h, 24h, 48h

Absorbed dose to blood for ^{177}Lu

$$D_{Bl}(t) = A_0 \cdot (85.3 \frac{Gy \cdot ml}{GBq \cdot h} \cdot \tau_{per\ ml\ Bl}(t) + \frac{0.00185}{weight^{2/3}} \frac{Gy \cdot kg^{2/3}}{GBq \cdot h} \cdot \tau_{WB}(t))$$

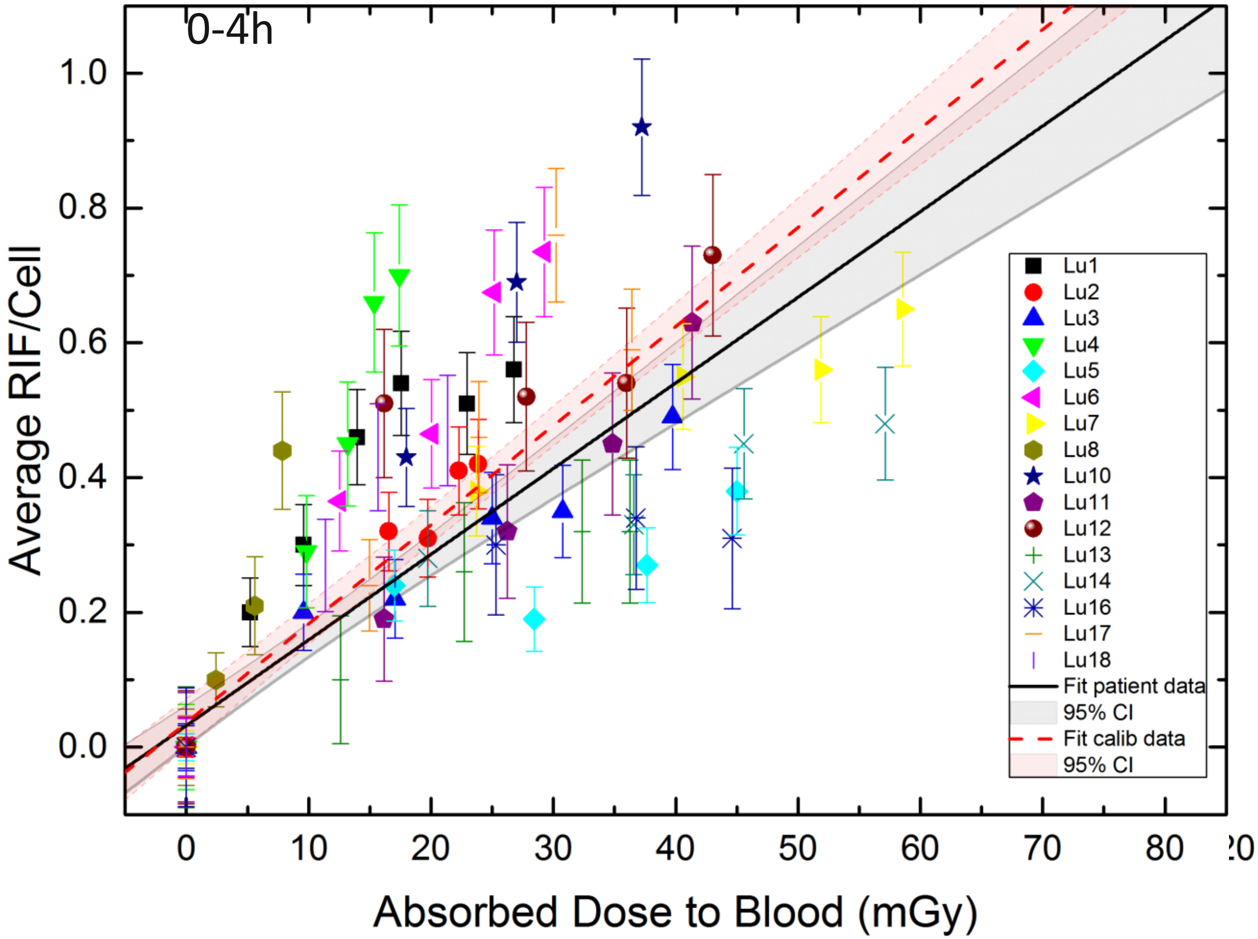


Mean absorbed dose to the blood after 48h (all patients):

- D(48h) = (78 ± 16) mGy
- 50% already reached after 10h

RIF as a function of the absorbed dose to blood: ^{177}Lu

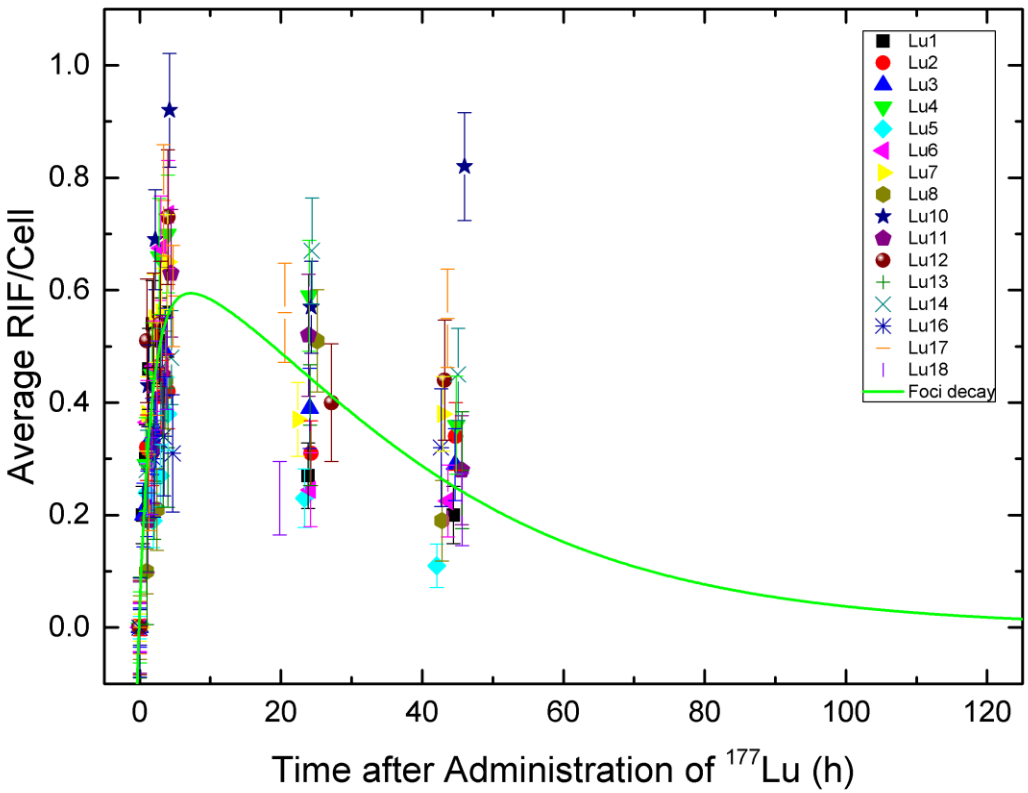
- Increase in the first 4h, decrease thereafter
- Linear function of the absorbed dose in the first 4 hours



Modelling the time-dependency of the focus induction and disappearance: PRRT

$$N(t) = (a + m \cdot b \cdot D_{Bl}(t)) \cdot e^{-\lambda \cdot t}$$

- a, b: constants taken from in-vitro calibration
- m: Adjustable parameter to account for the variability in the patient dosimetry with respect to the *in-vitro* calibration function
- $D_{Bl}(t)$: absorbed dose to blood
- λ: repair rate



- maximum
  - t=7.2h
- mean value λ
  - $(0.038 \pm 0.019)\ h^{-1}$

Results

- Motivation
- Basics
  - DNA damage
  - Calculation of absorbed dose to the blood
- Results
  - In-vitro calibration
  - In-vivo patient study: ^{177}Lu-therapy
  - **In-vivo patient study: ^{131}I-therapy**
- Summary

DNA Damage in Peripheral Blood Lymphocytes of Thyroid Cancer Patients After Radioiodine Therapy

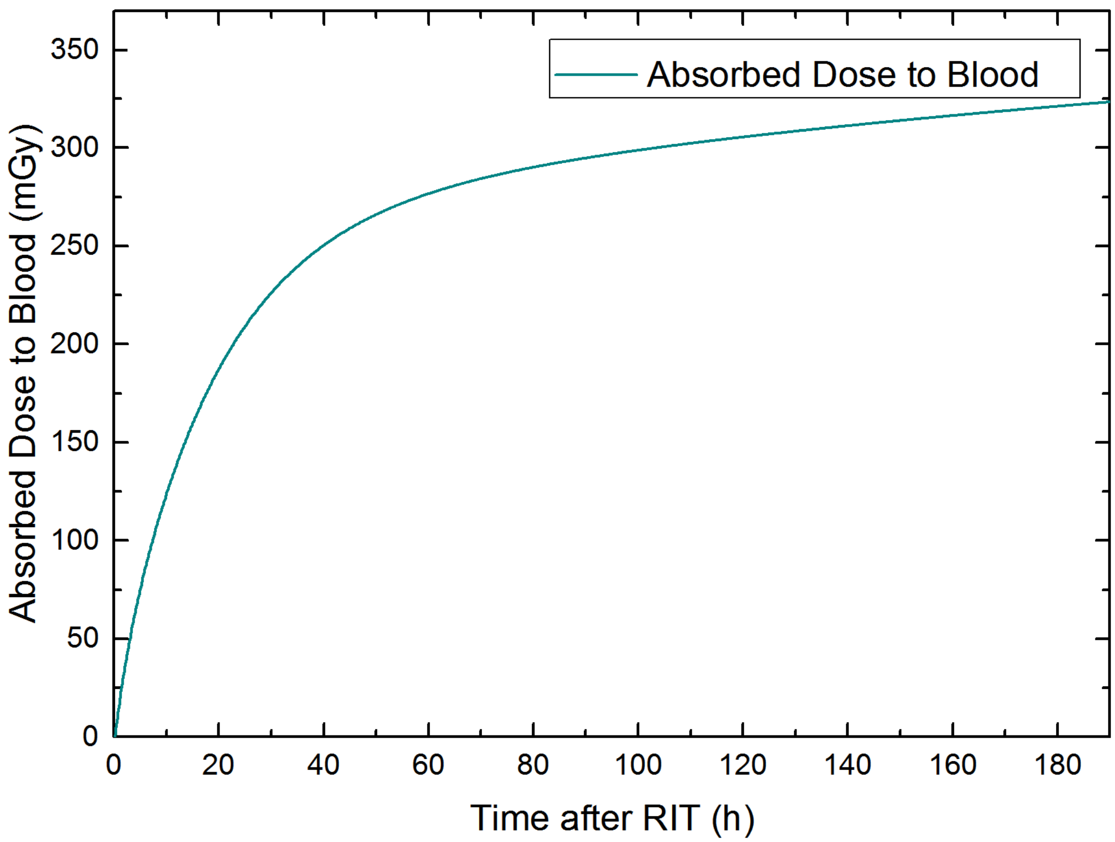
Uta Eberlein*[1], Harry Scherthan*[2], Christina Bluemel[1], Michel Peper[2], Constantin Lapa[1], Andreas Konrad Buck[1], Matthias Port[2], and Michael Lassmann[1]

Patients during radioiodine therapy (RIT)

- ^{131}I for the treatment of differentiated thyroid cancer (DTC)
  - After resection of the thyroid
  - Ablation of thyroid remnants
- 20 patients
  - 1^{st} RIT
  - Administered activity: (3.5 ± 0.3) GBq
- Blood withdrawal
  - Background sample before therapy
  - 1h, 2h, 3h, 4h, 24h, 48h, 72h, …

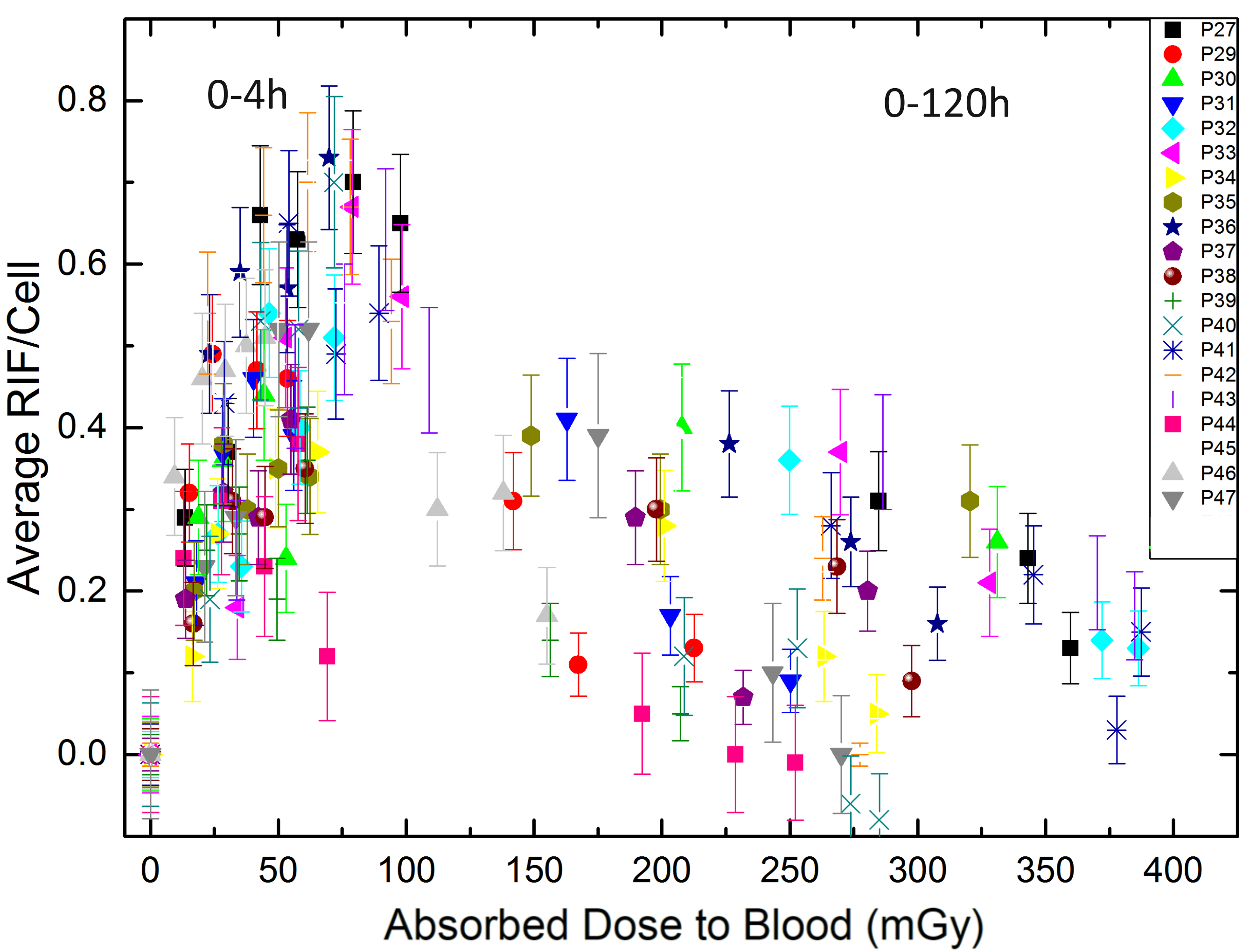
Absorbed dose to blood for ^{131}I

$$D_{Bl}(t) = A_0 \cdot \left(108.0 \frac{Gy \cdot ml}{GBq \cdot h} \cdot \tau_{per\ ml\ Bl}(t) + \frac{0.0188}{weight} \frac{Gy \cdot kg^{2/3}}{GBq \cdot h} \cdot \tau_{WB}(t)\right)$$



- Mean absorbed dose to the blood after 48h and t→∞ (all patients):
  - D(48h) = (263 ± 63) mGy
  - D(∞) = (367 ± 105) mGy
  - 50% of D(∞) reached only after 20h

RIF as a function of the absorbed dose to blood: ^{131}I

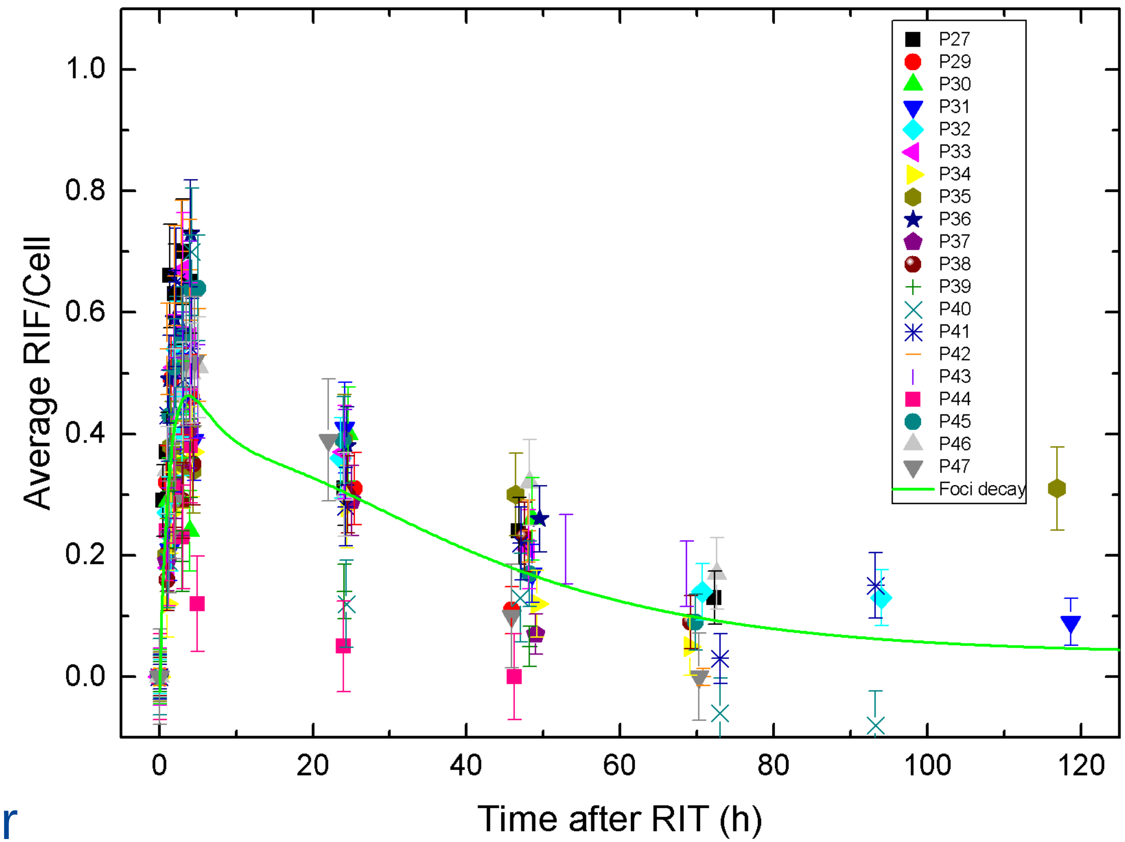


- Increase of RIF in the first 2-3h
- Flattening of the curve
- Decrease after 24h

Modelling the time-dependency of the focus induction and disappearance: DTC

$$N(t) = (a + m \cdot b \cdot D_{Bl}(t)) \cdot (k \cdot e^{-\lambda \cdot t} + (1-k)e^{-\nu \cdot t})$$

- fast repair rate
  $\lambda = (0.33 \pm 0.01)\ h^{-1}$
- slow repair rate
  $\nu = (0.04 \pm 0.02)\ h^{-1}$
- maximum
  - t= 3.2h
- fraction of damage assigned to the fast repair rate k = 76%
- fast repair induced when D> 20 mGy in the first hour after administration



Summary

- In-vitro calibration
  - **Linearity** between radiation induced foci (RIF) and absorbed dose could be confirmed

- DNA double strand break biomarkers γ-H2AX and 53BP1 were analyzed in lymphocytes of patients during their first
  - peptide receptor radionuclide therapy (PRRT)
  - radioiodine therapy (RIT) of differentiated thyroid cancer (DTC)

- The number RIF as a function of time was characterized by:
  - a **linear dose-dependent increase**
  - and a **multi-exponential decay function** characterizing different rates of DNA repair

- If the absorbed dose to the blood exceeds 20 mGy in the first hour
  - on-set of a **fast repair component** (**only** observed in **DTC** patients) resulting in a bi-exponential repair function
  - otherwise a **mono-exponential function** describes the repair of the double strand breaks better

Thank you for your attention!

Thanks to all people involved in this project

Prof. Michael Laßmann

Prof. Tcholpon Djuzenova

Prof. Andreas Buck

Prof. Harry Scherthan

DFG

DFG

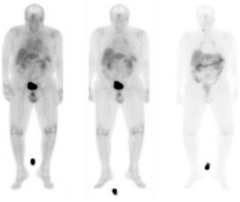
Dr. Christina Blümel

Dr. Constantin Lapa

Dr. Rudolph Werner

Ward team

Patients and volunteers



Inge Grelle

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