A $^{67/64}$Cu-mixture as a therapeutic alternative to pure ^{67}Cu

De Nardo L[1,2] , Pupillo G[3], Mou L[3], Esposito J[3], Rosato A[4,5], Meléndez-Alafort L[4]

[1]DFA, University of Padua. [2]INFN-Padua. [3]INFN-LNL, Legnaro (Padua). [4] IOV-IRCCS, Padua. [5] DISCOG, University of Padua.

Aim

- ^{64}Cu and ^{67}Cu, are currently considered among the most promising radionuclides for both diagnosis and therapy of cancers.
- ^{64}Cu is already commercially available, as it can be produced with high specific activity by using proton beams available at low energy (i.e. 18-24 MeV) cyclotrons.

	Half-life [h]	Decay (%)	Main emissions (%) [KeV]
^{64}Cu	12.72	β^- (38.5%)	β^- 579 (38.5%)
		β^+ (17.5%)	β^+ 653 (17.5%)
		EC (44%)	γ 511 (35%) γ 1346 (0.5%)
^{67}Cu	61.83	β^- (100%)	β^- 562 (20%) β^- 468 (22%) β^- 377 (57%)
			γ 185 (49%) γ 91-93 (23%)

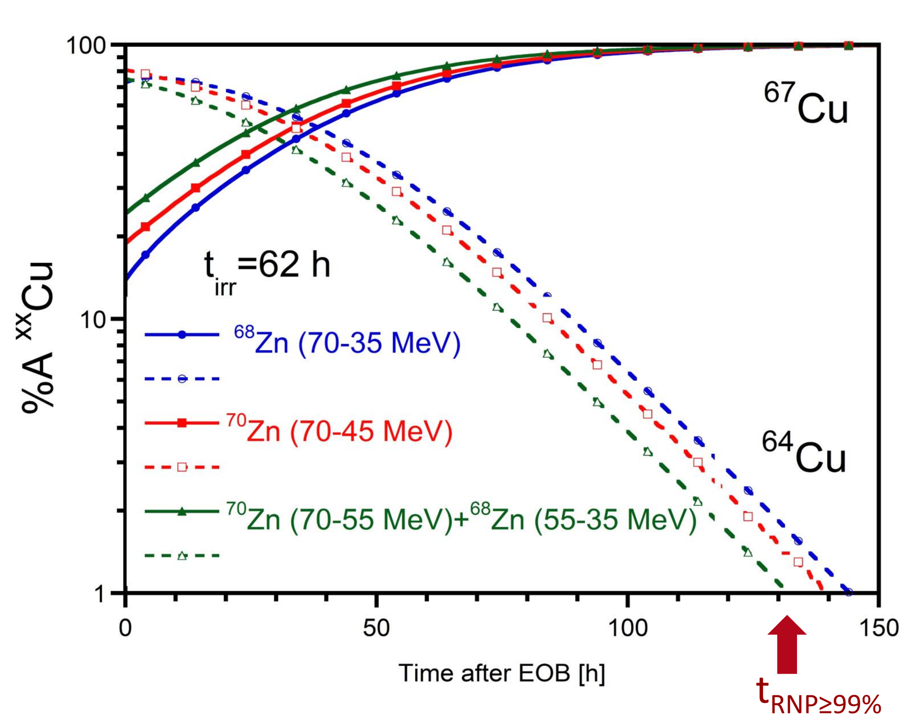
- On the other hand, high yield production of ^{67}Cu is difficult, due to the co-production of other Cu-isotopes, especially ^{64}Cu.
- To address this issue, currently preventing the spread use of ^{67}Cu in preclinical as well as clinical research programs, the possibility of using a mixture of ^{64}Cu and ^{67}Cu radioisotopes for therapeutic applications has been considered.

Methods

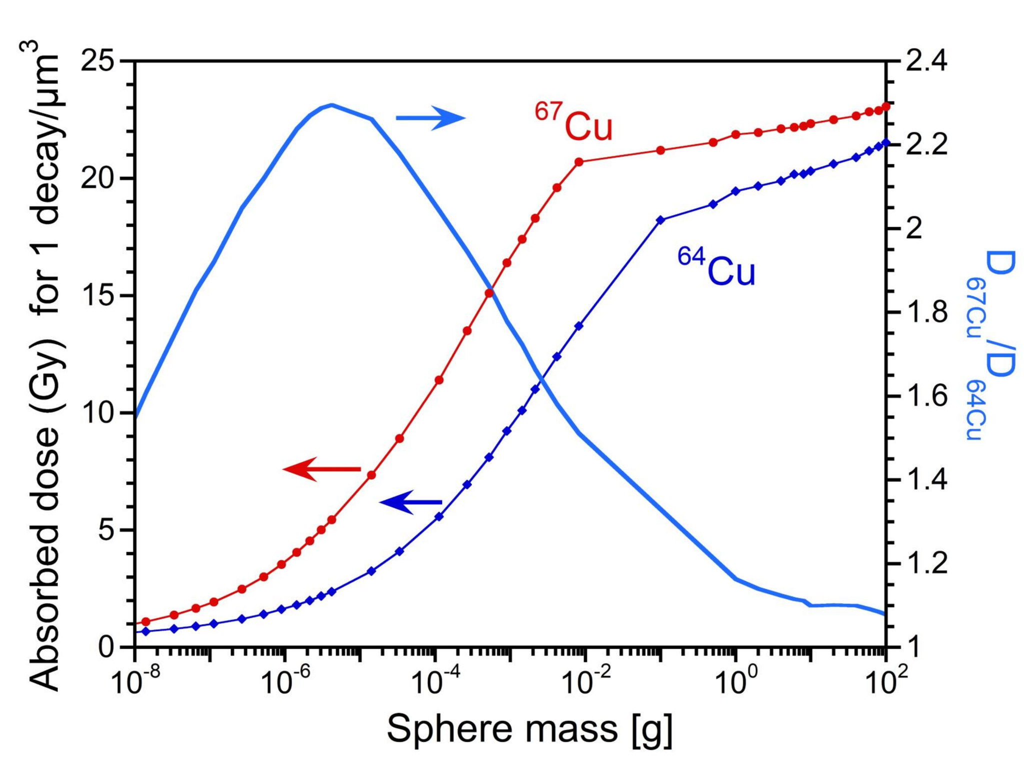
- Copper radioisotopes yields were calculated with the IAEA tool ISOTOPIA [1] by considering both experimental and calculated nuclear cross sections and proton beam irradiation of both ^{70}Zn and ^{68}Zn targets under different energy ranges and irradiation times [2].
- A simple spherical model [3-4], representing tumours of different sizes, was used to calculate the absorbed dose for uniformly distributed ^{64}Cu, ^{67}Cu and $^{67/64}$Cu mixture.
- The $CuCl_2$ biokinetic model published by ICRP 53 [5] was used to assess the human absorbed dose to healthy organs due to ^{64}Cu, ^{67}Cu and $^{67/64}$Cu mixture with the OLINDA software [4].

Results

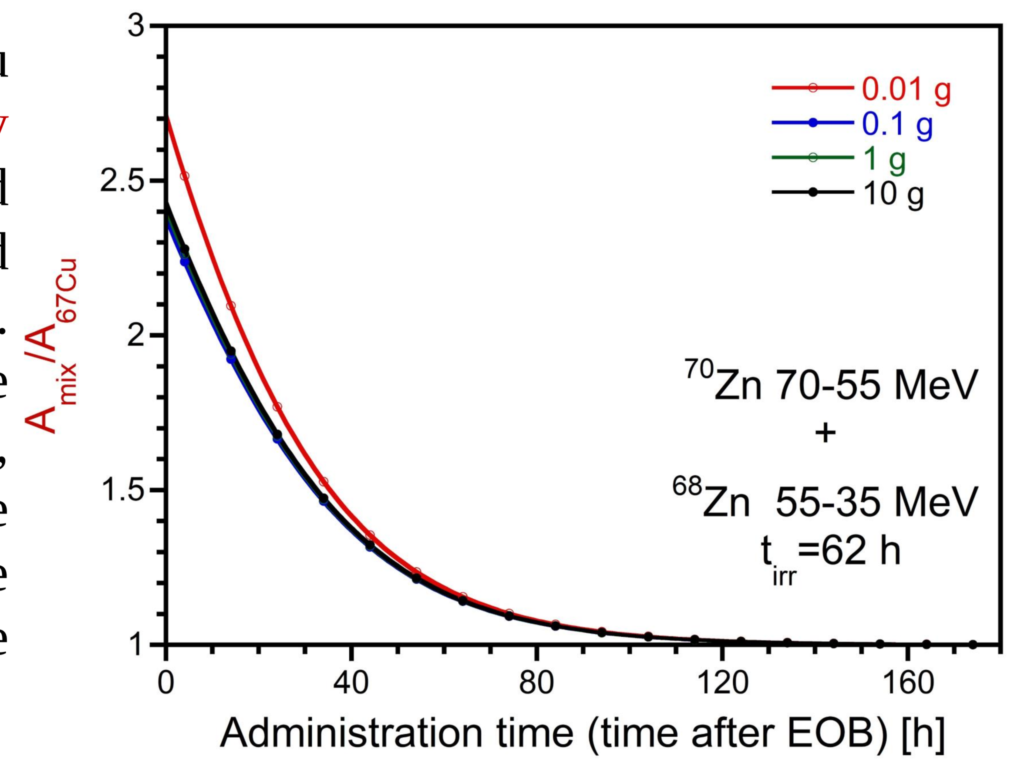
- The produced activity of ^{64}Cu is always greater than that of ^{67}Cu at the end of bombardment (EOB). However, due to the different half-lives of the two radioisotopes, the % of ^{64}Cu activity in the total decreases with time after EOB, while that of ^{67}Cu increases.



- Considering ^{64}Cu as an impurity (besides ^{61}Cu and ^{60}Cu) with respect to the ^{67}Cu production process, the waiting time necessary to achieve a radionuclidic purity (RNP) ≥99% would be $t_{RNP\geq99\%}$ =120-145 h, causing a decay of about 75-80% of the ^{67}Cu produced activity.
- By comparing the absorbed doses to a sphere model due to uniformly distributed ^{64}Cu and ^{67}Cu, it was found that ^{64}Cu administered activity must be about five times higher than that of ^{67}Cu to obtain the same absorbed dose for tumour mass 0.01-10 g and about ten times higher for smaller ones.



- By administration of a $^{67/64}$Cu mixture, a supplemental activity (A_{mix}/A_{67Cu}) is therefore required to get the same tumour absorbed dose produced by pure ^{67}Cu. A_{mix}/A_{67Cu} depends on the time of injection of the mixture, decreasing with increasing time after the EOB, due to the increasing % of ^{67}Cu in the mixture.

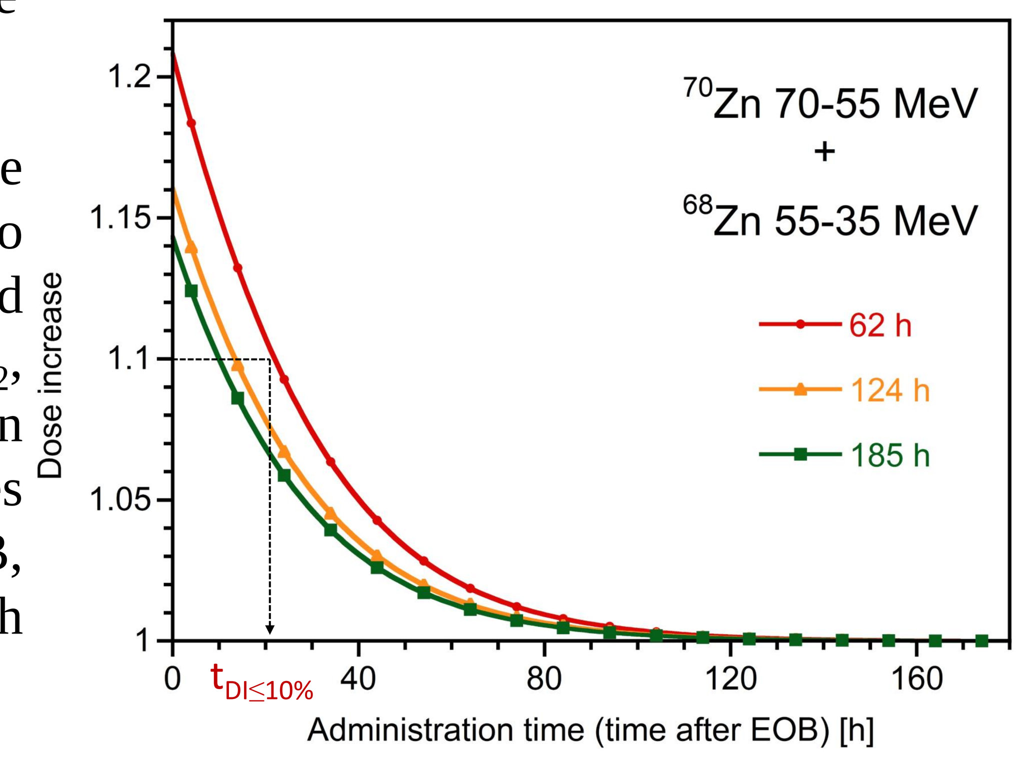


- Healthy organs absorbed dose factors for $^{67}CuCl_2$ are 3-6 times greater than for $^{64}CuCl_2$, resulting in an effective dose (ED) increment of 3.8.
- Absorbed dose per unit of administered activity of the $^{67/64}CuCl_2$ mixture increases with time after the EOB, due to the rising % of ^{67}Cu.

$^{xx}CuCl_2$ organ absorbes doses (mGy/MBq)

Target organ	$^{67}CuCl_2$		$^{64}CuCl_2$	
	Male	Female	Male	Female
Brain	0.483	0.537	0.108	0.12
Kidneys	0.263	0.301	0.0659	0.077
Liver	1.780	2.270	0.482	0.612
Pancreas	0.149	0.206	0.0413	0.0624
Total body	0.101	0.134	0.0231	0.0327
ED(mSv/MBq)	***0.131***	***0.168***	***0.0351***	***0.0444***

- The supplemental activity of the $^{67/64}CuCl_2$ mixture, required to get the same tumor absorbed dose produced by $^{67}CuCl_2$, triggers a dose increase (DI) in healthy organs which decreases with time after the EOB, becoming ≤10% between 10-35 h ($t_{DI\leq10\%}$) after the EOB.



^{67}Cu activity at EOB and at $t_{RNP\geq99\%}$ compared with $^{64/67}$Cu activity at $t_{DI\leq10\%}$)

Target and energy range [MeV]	t_{irr} [h]	^{67}Cu at EOB [MBq/µA]	$t_{RNP\geq99\%}$ [h]	^{67}Cu at $t_{RNP\geq99\%}$ [MBq/µA]	$t_{DI\leq10\%}$ [h]	$^{64/67}$Cu at $t_{DI\leq10\%}$ [MBq/µA]
^{68}Zn: 70-35	62	1240.1	145	244.1	35	1801.8
	124	1859.4	136	404.8	26	3018.5
	185	2165.2	133	487.5	23	3594.2
^{70}Zn: 70-45	62	1751.7	139	368.7	30	2711.6
	124	2626.5	131	604.8	21	4542.8
	185	3058.5	128	728.3	18	5409.0
^{70}Zn: 70-55 + ^{68}Zn: 55-35	62	1881.3	132	428.3	22	3223.4
	124	2820.9	123	710.5	13	5400.9
	185	3284.9	120	855.6	10	6430.0

Conclusions

- A mixture of cyclotron produced $^{67/64}$Cu radioisotopes proved to be an alternative solution for the therapeutic use of $CuCl_2$ with minimal dose increase to healthy organs as compared to pure ^{67}Cu.
- Among all the production routes investigated, 185 h irradiation of a ^{70}Zn+^{68}Zn target in the 70-35 MeV proton energy range provides the maximum amount of activity, the shortest waiting time necessary to keep the healthy organ dose increase below 10% and less than 1% of ^{61}Cu and ^{60}Cu impurities, consequently it is the best option [2].
- Future investigations on $^{67/64}$Cu radioisotopes will be performed in the framework of CUPRUM-TTD project (2023-2025), funded by INFN-CSN5.

References

(1) ISOTOPIA,Medical Isotope Browser. IAEA nuclear data section. https://www-nds.iaea.org/relnsd/ isotopia/isotopia.html
(2) De Nardo L *et al*. [2022] Med Phys 49(4) 2709-2724, https://doi.org/10.1002/mp.15524
(3) Vaziri B *et al.* J [2014] Nucl Med.;55:1557-1564. https://doi.org/10. 2967/jnumed.113.131037
(4) Stabin M, Farmer A [2012] J Nucl Med, 53 (1): 585
(5) ICRP Publication 53 [1988] Ann. ICRP 18 (1-4)

20th European Symposium on Radiopharmacy and Radiopharmaceuticals

ESRR'22 – NOVEMBER 24 – 27, 2022