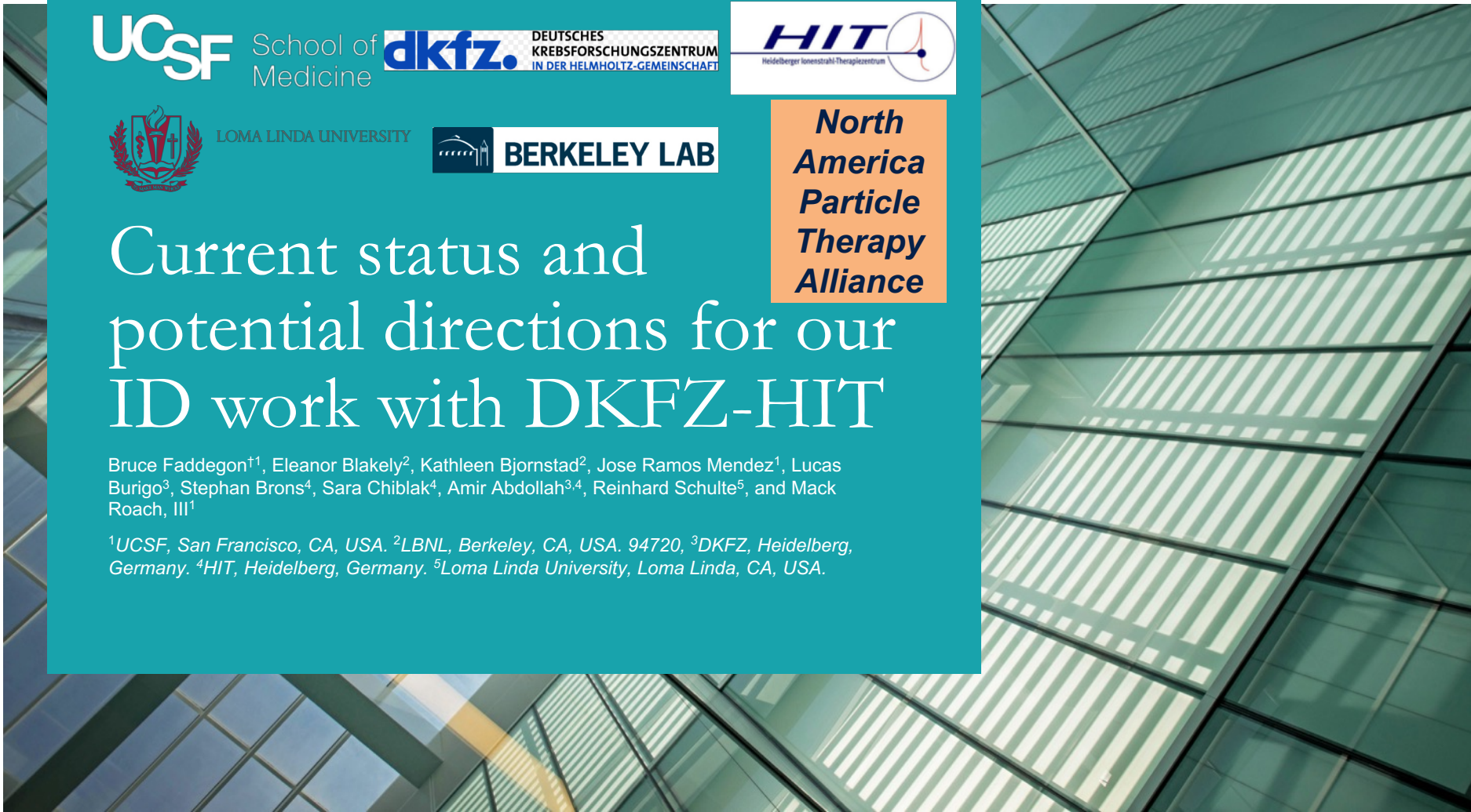

North America Particle Therapy Alliance

Current status and potential directions for our ID work with DKFZ-HIT

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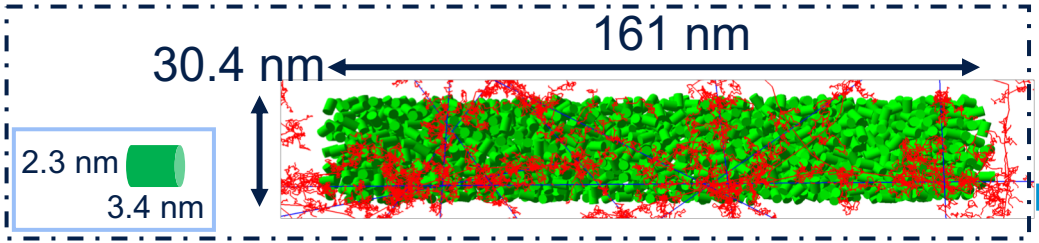
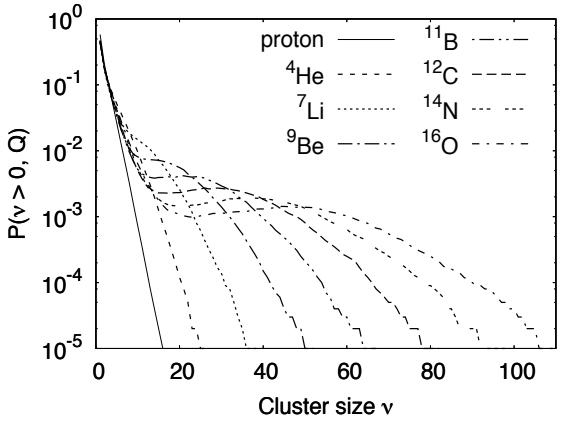
Ion-therapy planning that incorporates ionization detail

- Background and motivation
- Experimental procedure and results
- Conclusions
- **Future**
- Acknowledgments:
  - Primary human clival chordoma cell line UM-Chor1 kindly provided by the Chordoma Foundation
  - Partial support from NIH 1P20CA183640 grant (PI Mack Roach III)

ID: Ionization Detail



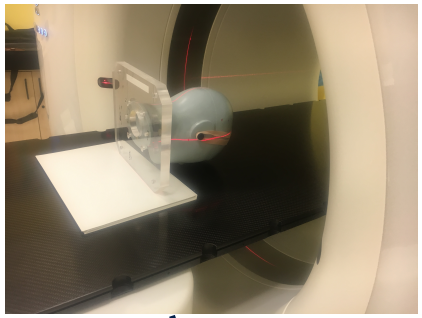


Conditional ICSD for light ions with 1 MeV/u.

Motivation

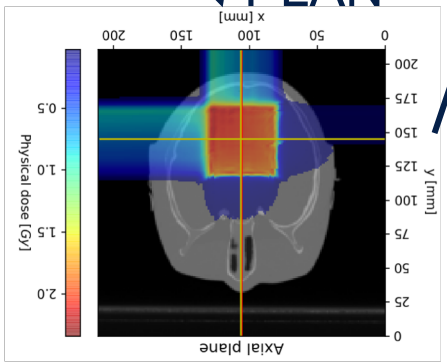
- Details of the pattern of ionization deposition (ID) along ion tracks are important to the biological effect, such that knowledge of the ID may improve individual patient treatment plans
- However, ID calculation relies on time consuming track structure simulation
- We incorporate pre-calculated ID into the treatment plan, in this case to increase uniformity in the density of large clusters across the target volume
- What is the best choice of ID? Ideally, this is based on radiology experiments

Nick experiment at HIT

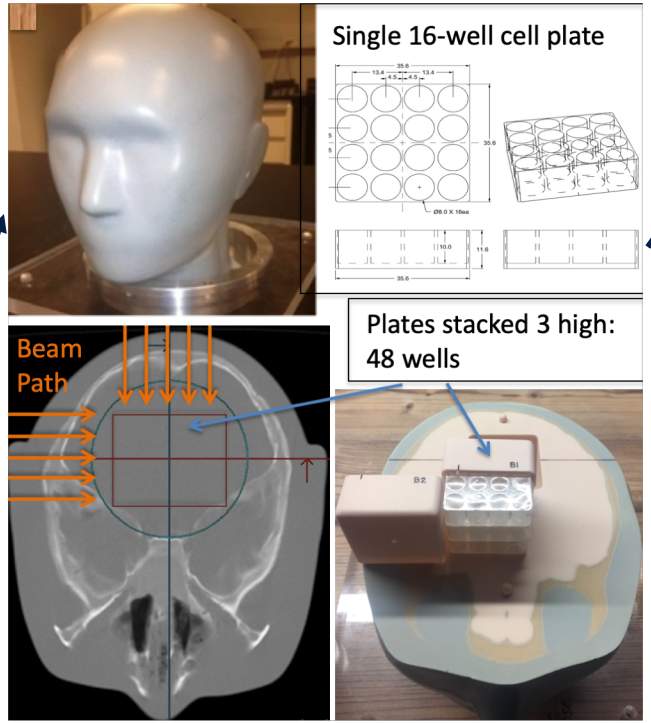


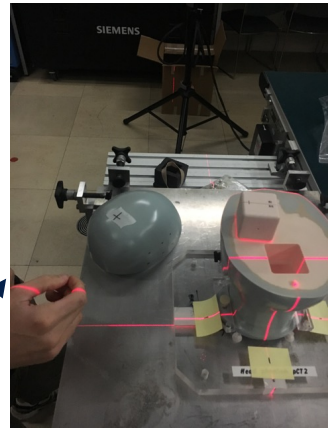
SCAN

PLAN



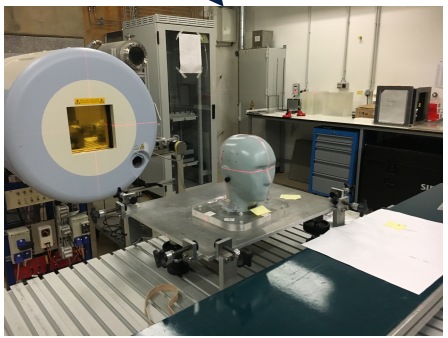
Place cells in cube: Primary human clival chordoma cell line UM-Chor1





POSITION

TREAT



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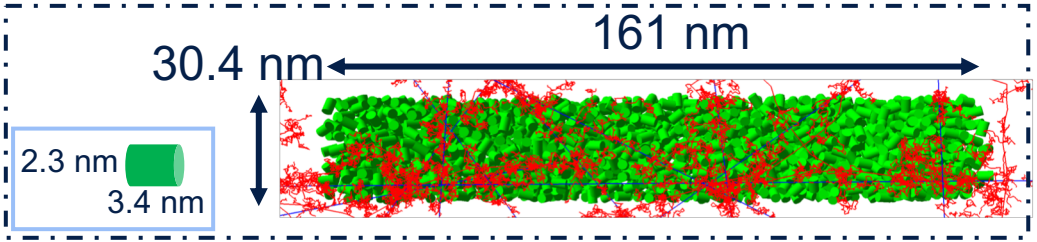
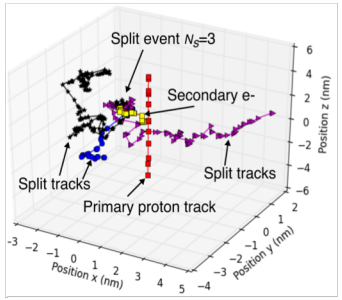
Pre-calculated ID

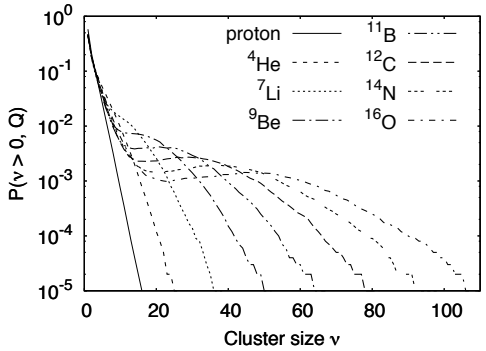
Track-structure simulation with TOPAS-nBio/Geant4-DNA





Flagged particle splitting

Ramos-Méndez et. Al. *Phys. Med. Biol.* 62(15), 5908-25, 2017



Conditional ICSD for light ions with 1 MeV/u.

$$m_1(Q) = \frac{\sum_{\nu=2}^{\infty} \nu\, P(\nu|Q)}{\sum_{\nu=2}^{\infty} P(\nu|Q)}$$

$$f_3(Q) = \frac{\sum_{\nu=3}^{\infty} \nu\, P(\nu|Q)}{\sum_{\nu=2}^{\infty} P(\nu|Q)}$$

Energy dependent m_1 or f_3

Bueno et. Al. *Phys. Med. Biol.* 60(21), 8583, 2015
Alexander et. Al. *Eur. Phys. J D*. 69(216), 2015

Ramos-Méndez et al, *Phys Med Biol* 63:235015-28, 2018

UCSF

Use of pre-calculated ID for voxel-based ID estimation

Macroscopic approach and verification with track structure simulations

In a voxel *i*:

$$ID_{\mathrm{d}}^{i}(Q) = \frac{\sum_{j,p} q_j^p(E_j)\,\Delta E_j}{\sum_j \Delta E_j}$$

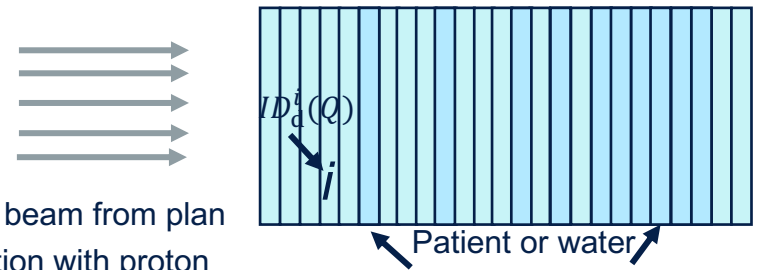
Interpolated m_1 or f_3 at energy E_j

Energy deposited at event j

Similar approach was used in Alexander et. Al. *Phys. Med. Biol.* 60(13), 9145, (2015) for cellular-size simulations.

Ramos-Méndez et al, *Phys Med Biol* 63:235015-28, 2018

Condensed-history simulation

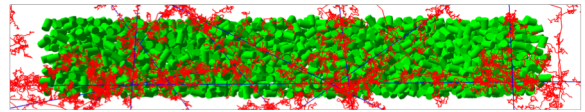


- Particle beam from plan
- Verification with proton SOBP of 10.6 cm range, 2 cm modulation and carbon SOBP of 26 cm range

Phase spaces

Track-structure simulation

(Geant4-DNA/TOPAS-nBIO)



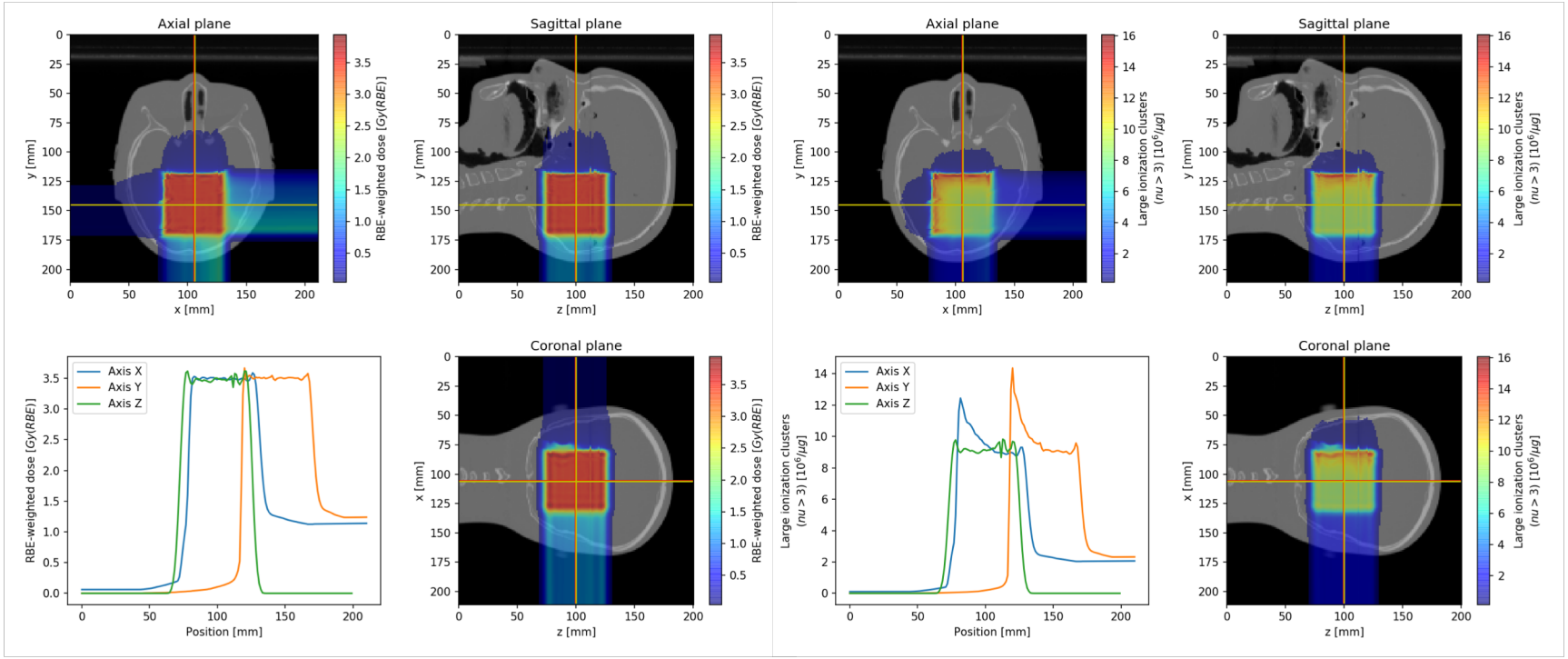
Shrunken phase space at slice position *i*

Treatment plans: LEM alone

12C PA: 112.6 - 222.3 MeV/u
12C RL: 95.7 - 196.2 MeV/u

RBE-weighted dose

ID: Large cluster density



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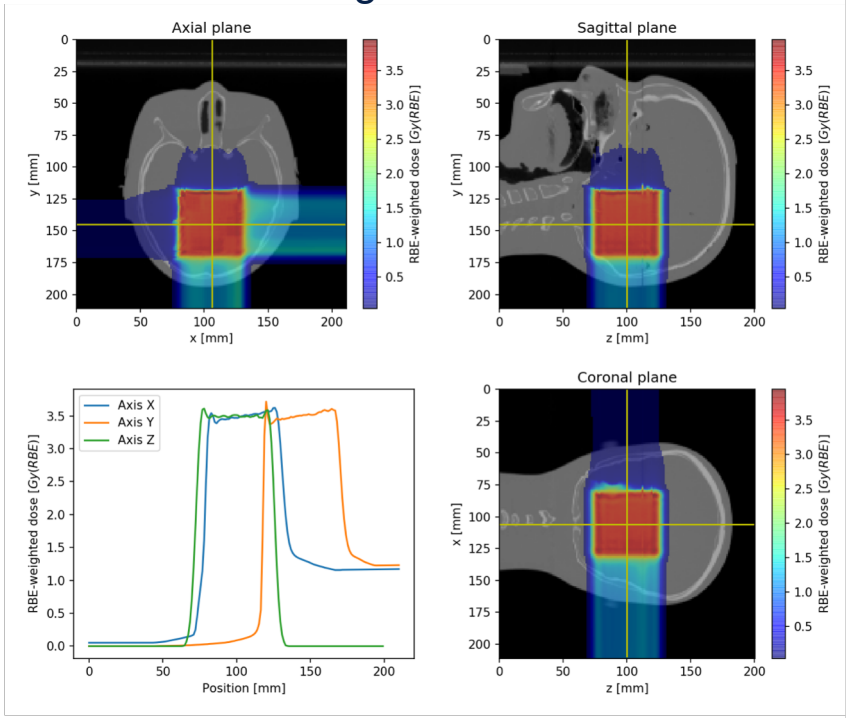
Treatment plans: Uniform ID

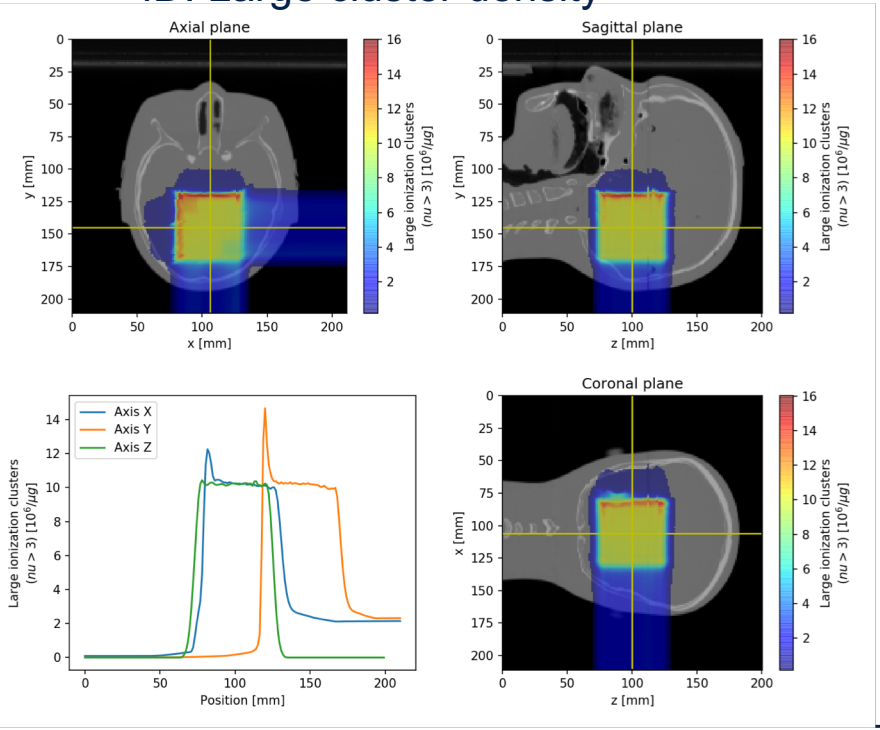
12C PA: 100.1 - 222.3 MeV/u
12C RL: 88.8 - 196.2 MeV/u

Simultaneous optimization of LEM and ID using (MatRad from DKFZ)

RBE-weighted dose



ID: Large cluster density



Burigo et al, Phys Med Biol 64:015015-27, 2019

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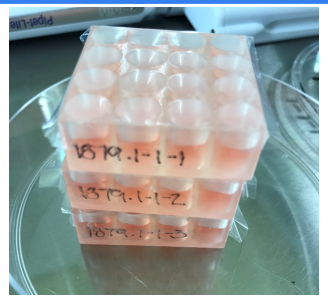
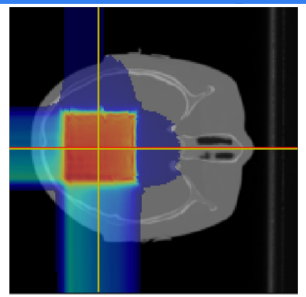
Results: LET (keV/μm) for LEM alone

LET statistical uncertainty of 8% (1 standard deviation)

	TOP WELLS				MIDDLE WELLS				BOTTOM WELLS			
	A1	B1	C1	D1	A2	B2	C2	D2	A3	B3	C3	D3
a	51	51	54	63	52	51	51	54	56	55	55	58
b	41	41	48	58	38	38	41	51	39	39	42	51
c	33	34	44	56	32	33	40	52	33	34	41	52
d	30	33	44	55	29	33	40	52	29	33	41	51

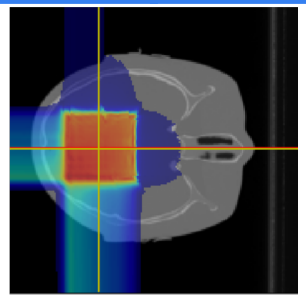




Results: LEM+ID result/LEM result

Average ID for each well for all 3 plates

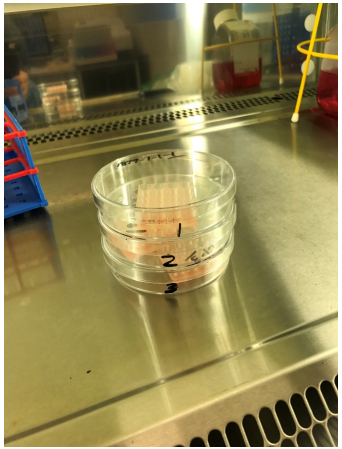
	LET ratio (± 0.04)				f3 ratio (± 0.006)			
	A	B	C	D	A	B	C	D
a	0.95	1.03	1.06	1.08	0.988	0.999	1.002	1.004
b	1.26	1.37	1.28	1.06	1.037	1.048	1.033	1.005
c	1.43	1.54	1.30	1.05	1.064	1.071	1.042	1.004
d	1.25	1.41	1.18	0.95	1.047	1.062	1.029	0.990

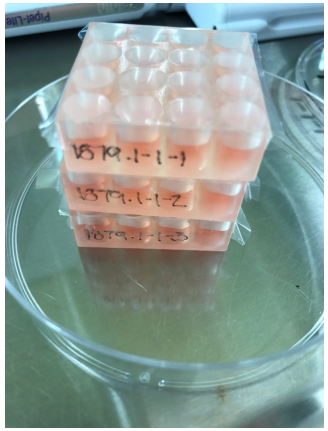


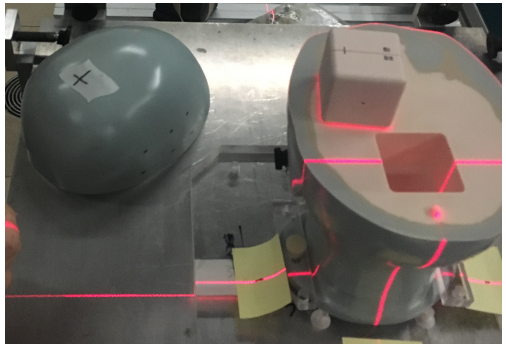
Results: HIT experiment

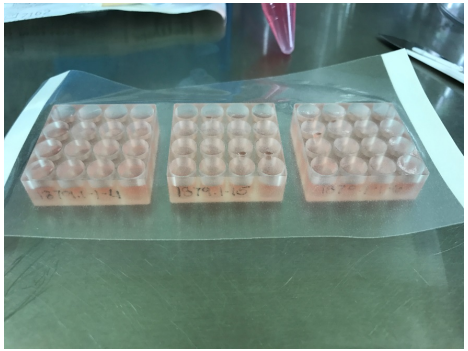
- A **high plating efficiency of 44.3%** was achieved at HIT, double of that at LBNL. This is under investigation with particular attention being paid to the different sources (US vs German) of the components of the growth media used.
- Survival was defined as **30 or more cells per colony** instead of the usual 50 to account for shorter time given for colonies to grow (colonies were crowded due to higher than expected plating efficiency, **~400 colonies per flask**)

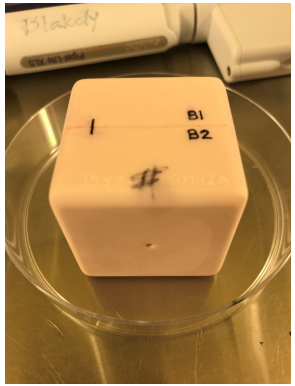
Nick Experiment

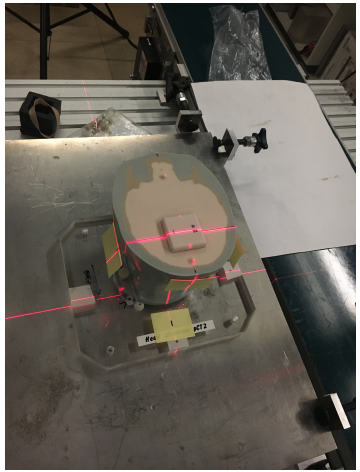












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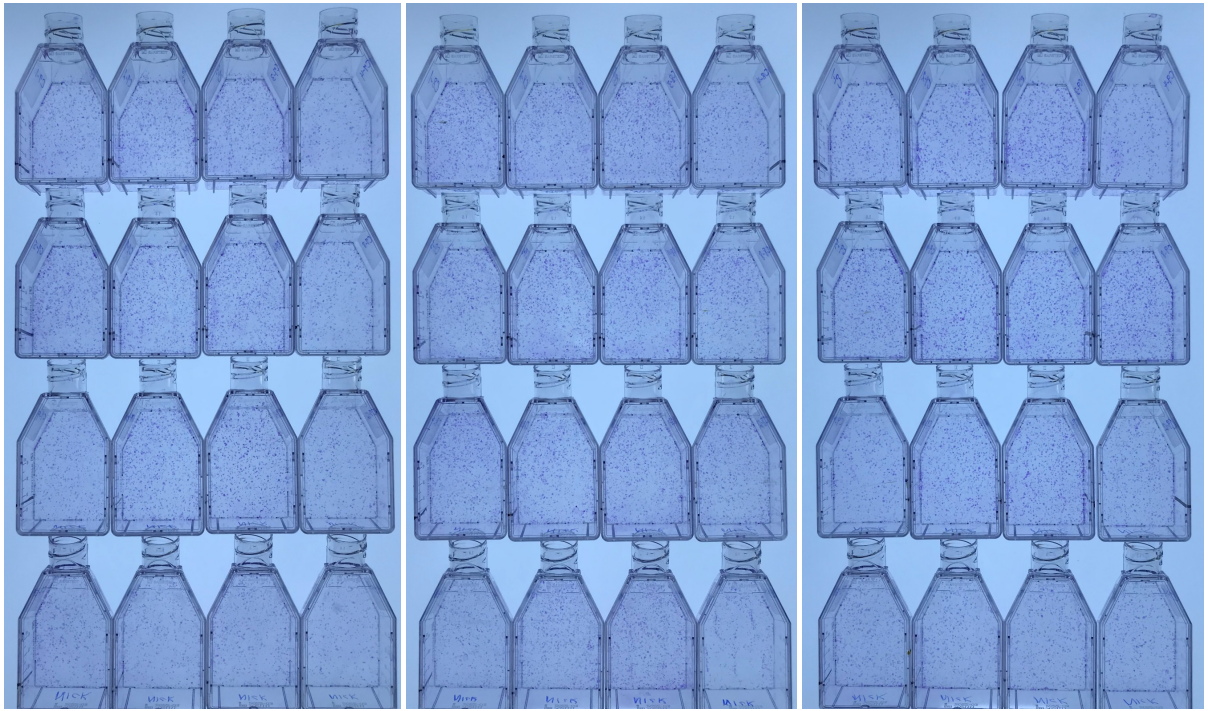
Results: Flasks for colony counts, LEM trial 2



TOP WELLS MIDDLE WELLS BOTTOM WELLS

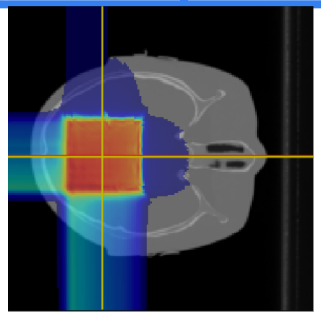
UCSF

Survival dependence on ID

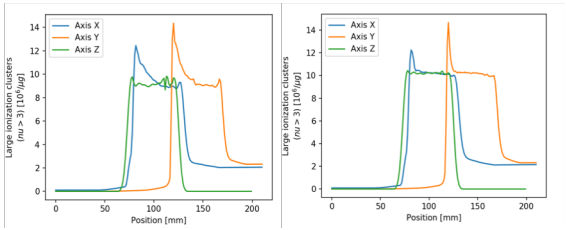
Ratio of LEM+ID result to LEM result averaged over all 3 plates

	Survival ratio (± 0.37)				f3 ratio (± 0.01)			
	A	B	C	D	A	B	C	D
a								
b		1.31	1.39			1.05	1.03	
c		1.61				1.07		
d	0.99	1.24	0.79	0.90	1.05	1.06	1.03	0.99

Survival averaged over 3 repeats x 3 wells in the stacked plates



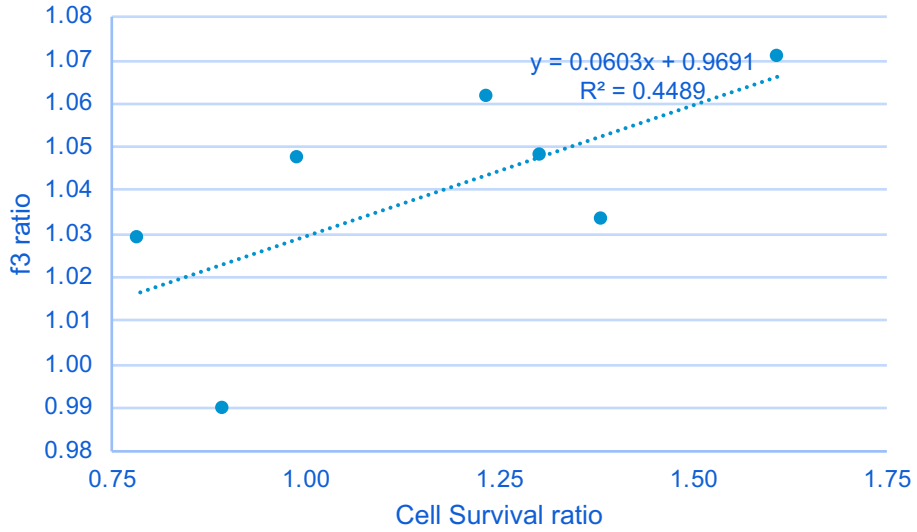
ID: RBE RBE+ID



UCSF

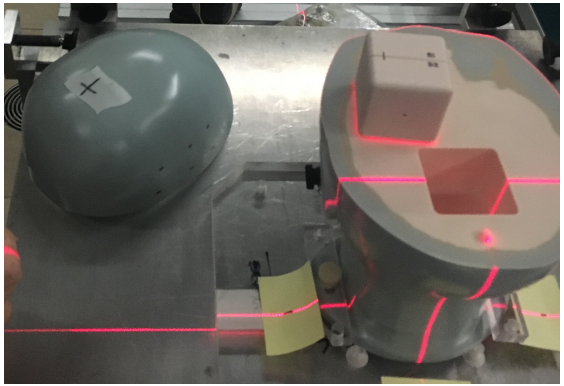
Survival dependence on ID

Ratio of LEM+ID result to LEM result averaged over all 3 plates



Conclusion

- Methodology has been established to compare measured and calculated biological effect across the target volume in an anthropomorphic phantom irradiated with clinically realistic treatment plans that incorporate ionization detail
- We are working on improving accuracy so that the method is capable of providing a clinically meaningful comparison between alternative methods of biologically-based treatment plans



Future of ID based treatment planning research

- Find alternative cell viability endpoint capable of providing a clinically meaningful comparison between alternative methods of biologically-based treatment plans:
  - Reliably measure a change in cell viability due to a 3% difference in dose with comparable ID
- Choose ID's from simple to complex that correlate with cell survival
  - Choice of ID is a juxtaposition of physics, chemistry, biology, and math (statistics)
  - Measure survival and cell viability dependence on various ID
- Perform Nick experiment for a selection of ID
  - Simultaneous optimization with clinical RTP systems (LEM, etc.)
  - Stand-alone ID-based treatment planning