Patient-derived Sarcospheres to Inform Precision Medicine with Repurposed FDA-approved Oncology Drugs

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Long-Term Goal

Repurpose FDA-approved Oncology Drugs

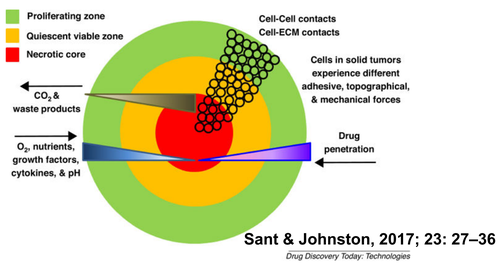
- Known Safety Profile
- Higher Success Rate, Faster & Cheaper than Developing New Drugs

Precision Medicine for Patients with Osteosarcoma

- Considerable Genetic Diversity Between Patients
  => Probably No Silver Bullet
- Need to Find the Best Drug for Each Patient
- Genome-based Precision Medicine Disappointing:
  No Driver Mutations or Transcriptional Signatures to Predict Drug Sensitivity
  ⇒Functional Precision Medicine
- Future:
  Combine Genome-based & Functional Precision Medicine

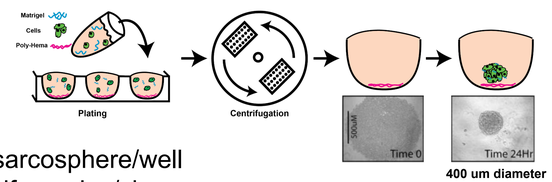
3D Spheroids as Patient-specific Avatars to Inform Functional Precision Medicine

- Predict Drug Responses in Other Cancers:
  Breast,[1,2] Lung,[3,4] Ovarian,[5,6] Glioma[7]
- Better Biology than Monolayers:



Sant & Johnston, 2017; 23: 27–36
Drug Discovery Today: Technologies

Making Osteosarcoma Spheroids (Sarcospheres) [8,9]



400 um diameter

1 sarcosphere/well
Uniform size/shape
Reasonable throughput
Low Tech

References

1. Halfter et al 2015, BMC Cancer 15:519
2. Halfter et al 2016 J Transl Med 14:112
3. Di Liello et al 2019 ESMO Open 4:e000536
4. Lee et al 2020 Cancers (Basel) 12:3394
5. Shuford et al 2019 Sci Rep 9:11153
6. Akerlund et al 2023 NPJ Precis Oncol 7:111
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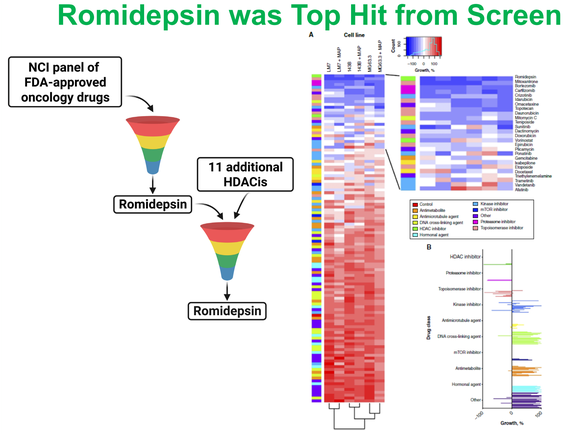
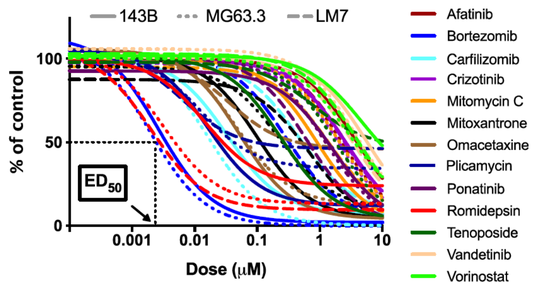
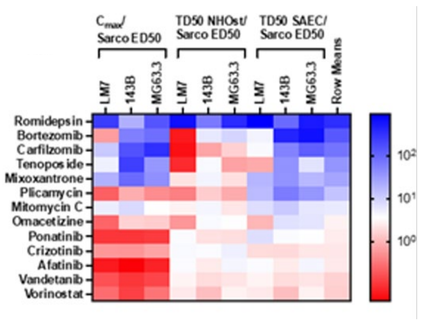
8. Seiden et al 2025 Cancer Res Commun 5:1821-1838
9. Collier et al 2018 Clin Orthop Rel Res 476:1400-1411

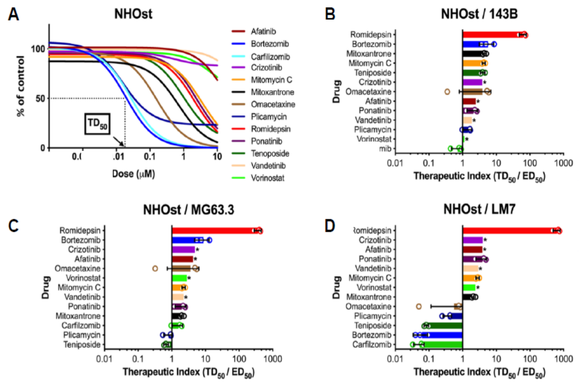
Cell Line Sarcospheres

Romidepsin was Top Hit from Screen of FDA-Approved Oncology Drugs [8]

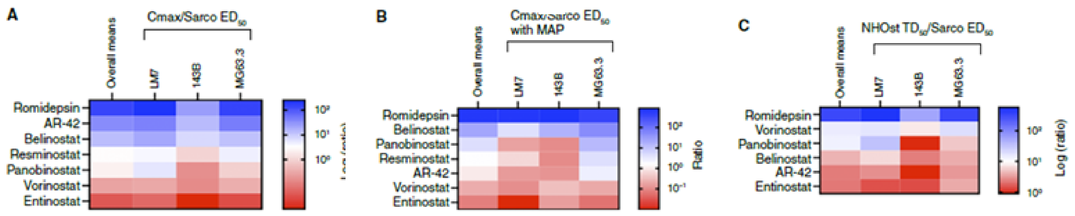




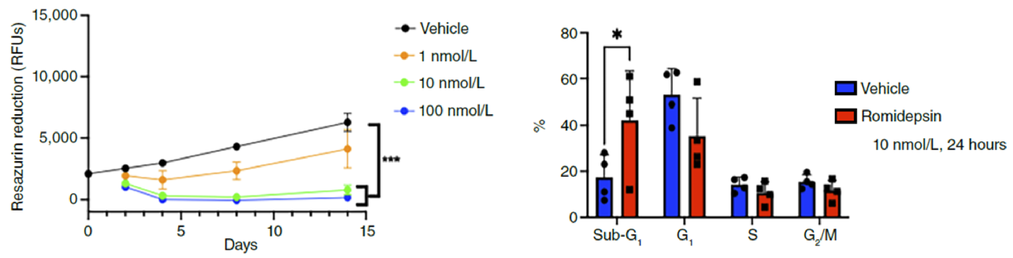




Romidepsin Out-performed 12 other HDACis: FDA-approved or in Clinical Trials [8]



Effects of Romidepsin on LM7 Sarcospheres were Durable and Associated with Increased Sub-G1 [8]



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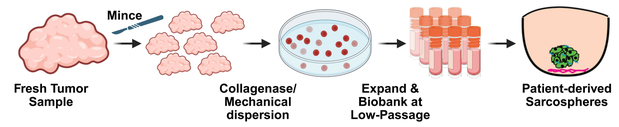
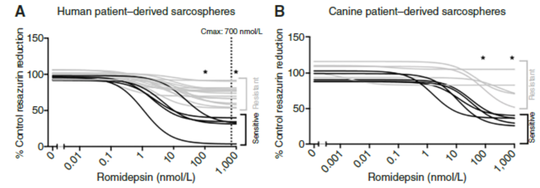
Patient-derived Sarcospheres



We Successfully Banked Cells from 56 of 58 Patients
We Successfully Made Sarcospheres from 28 of 28 Patients [8]

Sarcospheres from ~35% of Patients were Sensitive to Romidepsin at Clinically-achievable Levels [8]



Validation: Do patient-derived sarcospheres predict drug responses?

Source of Sarcospheres	Drugs to Test	Outcomes to Predict
Any	Any	Murine Models: Primary Tumors & Metastases
Biopsy: Human	MAP	Necrosis at Resection
Amputation: Canine	Carboplatin	Progression-free Survival & Overall Survival
Resection of Primary Tumor: Human	MAP	
Resection of Relapses	Same drug that patient will receive next	
Metastasectomy		
Clinical Trials: Human or Canine	Same drug as clinical trial	

YOUR HELP IS NEEDED TO VALIDATE THE SARCOSPHERE PLATFORM

1. Do you participate in sarcoma clinical trials (human or canine)?
2. Would you like to collaborate?
3. Can fresh tissue be obtained before patients receive trial drug?

IF ANSWER TO ALL 3 QUESTIONS IS YES:
Please contact Ed Greenfield: egreenf@IU.edu

Conclusions

Sarcosphere-informed precision medicine is a promising approach to find the best drug for each patient with osteosarcoma and could easily be extended to other sarcomas with poor prognosis and to ultra-rare sarcomas.