

Lessons Learned from 25 Years of Hunting for Cures

BIOUTAH 2020 Entrepreneur & Investor Summit

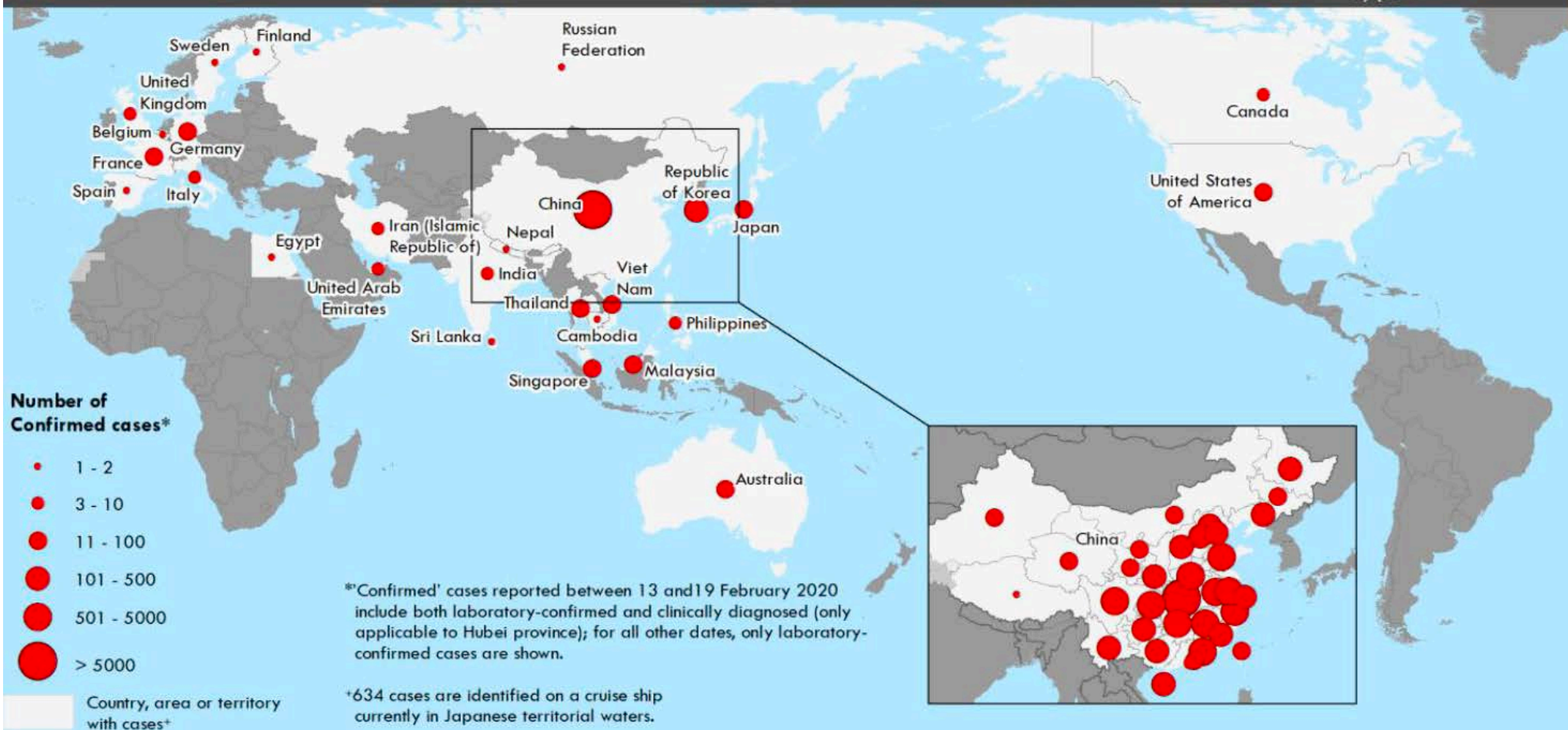
David Bearss Ph.D.

CEO Tolero Pharmaceuticals

February 28th, 2020

We Are Witnessing a Potential Global Health Crisis

Distribution of COVID-19 cases as of 21 February 2020



Data Source: World Health Organization, National Health Commission of the People's Republic of China
Map Production: WHO Health Emergencies Programme

Not applicable

0 2,500 5,000 km
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The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

- We work in a unique industry
- We strive to save millions of lives and help those suffering from disease to recover and lead more productive lives
- Our industry employs millions of people who are proud to participate in this crucial endeavor
- Although we are the recipients of lot of bad press (some of it deserved) the ongoing commitment of the research-based pharmaceutical industry to improve the quality of life for all of the world's people is the driving force for those of us in this industry

- More than 800,000 people work in the biopharmaceutical industry in the United States across a broad range of occupations, including scientific research, technical support, and manufacturing
- Directly and indirectly, the industry supports more than 4.7 million jobs across the United States.
- **There are only just over 3600 FDA approved drugs for human use**
- Getting a new drug approved is a very rare and historical event and new drug approvals ***change the world***

Just a Few Examples of Drugs that Have Changed our World

1. Penicillin
2. Insulin
3. Smallpox vaccine
4. Morphine
5. Aspirin
6. Polio vaccine
7. Chlorpromazine or thorazine
8. Chemotherapeutic drugs
9. HIV Protease inhibitors
10. Hormonal contraception

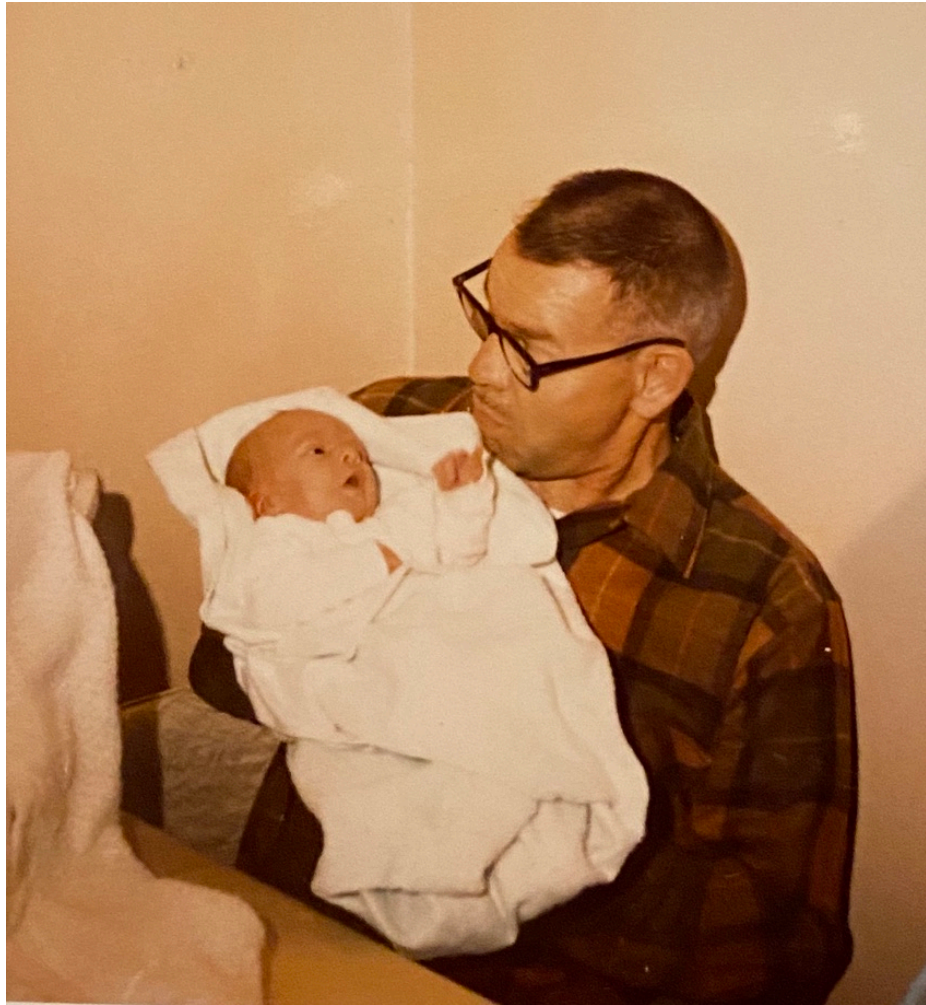
- Discovering and Developing Drugs is as Much Art as Science

“The reason is as simple as it is profound: there still are no clear scientific laws, engineering principles, or mathematical formulae that can guide an aspiring drug hunter all the way from idea to product...

...even though there have been a number of advances that make different components of the drug hunting process more efficient—such as receptor theory, rational design, recombinant-DNA engineering, pharmacokinetic testing (evaluating how a drug is processed by the body from ingestion to elimination), transgenic animal disease modeling (genetically engineering an animal’s DNA to mimic some aspect of human disease in order to test the drug on the animal instead of a human), high-throughput screening (the ability to rapidly evaluate thousands of compounds), and combinatorial chemistry (the ability to generate thousands or even millions of different chemical compounds in a single process in order to use them for testing).”

Kirsch, Donald R.. The Drug Hunters: The Improbable Quest to Discover New Medicines (p. 249). Arcade Publishing. Kindle Edition.

The only picture I have of me and my grandfather Glenn Bearss



I Learned a Lot from My Father

James G. Bearss Ph.D.



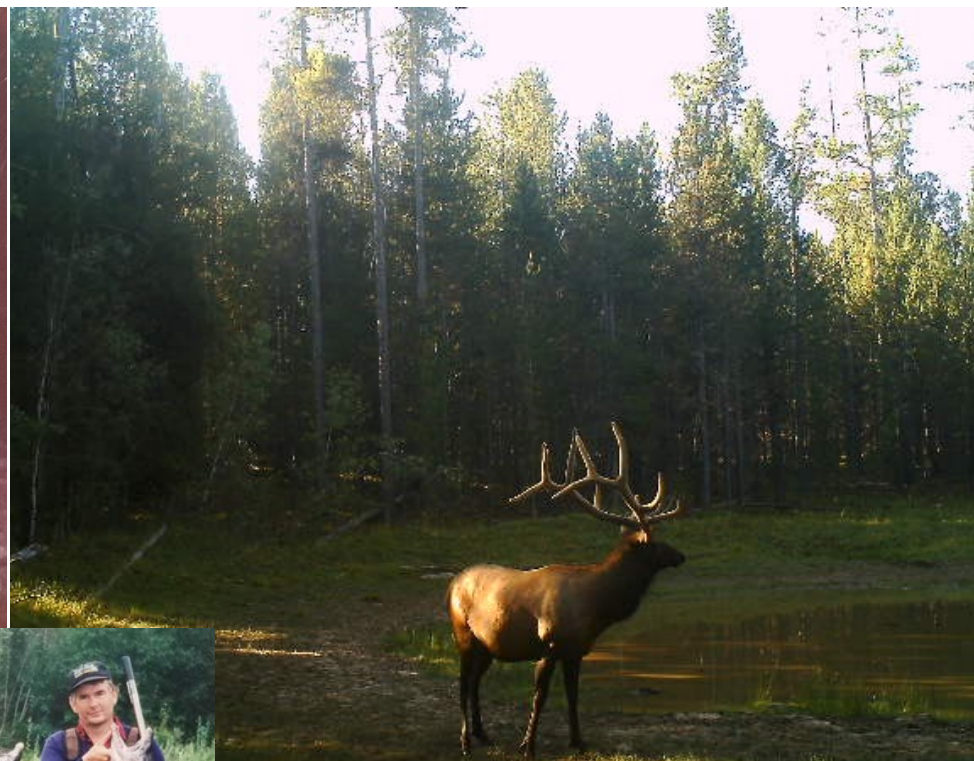
Even More Motivation; I Lost My Mother to Colon Cancer

My mother Renee Bearss



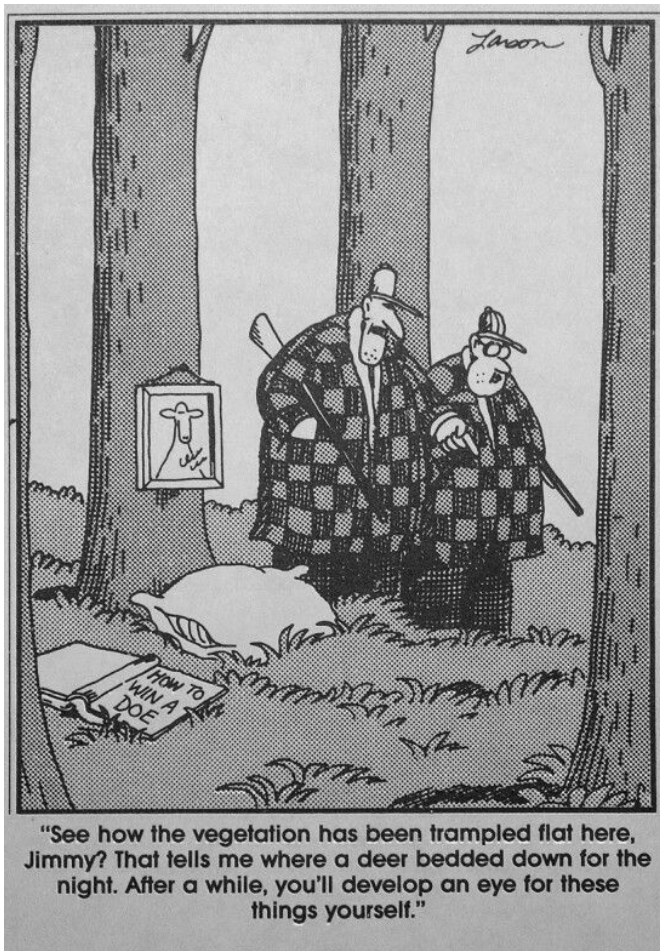
- I have never had a day when I was not excited to get up in the morning and try and make progress toward discovering new treatments for cancer
- I love what I do, and there is nothing more motivating to me than thinking I can change the world by finding new treatments for people suffering for serious diseases

I learned to hunt (and fish) from the best hunter I know: My Father-in-Law
Jerry Grover



What I Have Learned About Hunting is This:

- The best hunters are:
 - Relentless
 - Passionate
 - Always learning and trying new things



"OK, one more time and then it's off to bed for the both of you. ... 'Hey, Bob. Think there are any bears in this old cave?' ... 'I dunno, Jim. Let's take a look.'"

John Lamb, PhD

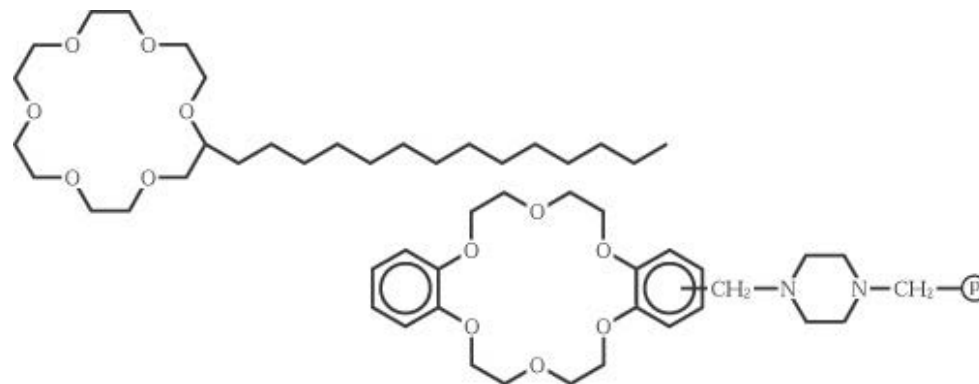


Original Articles

Alkoxyethyl-Substituted 18-Crown-6 and 21-Crown-7 Ligands: Synthesis, Complexation Properties, and Metal Ion Membrane Separations

Chuan Wang, Peter Huszthy, Jerald S. Bradshaw, John D. Lamb, Bogdan Olenyuk, David Bearss & Reed M. Izatt ...show less
Pages 1589-1607 | Published online: 23 Sep 2006

Download citation <https://doi.org/10.1080/01496399508010364>



My Early Years and the Discovery of Histone Deacetylase



Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 12845–12850, November 1996
Biochemistry

Transcriptional repression by YY1 is mediated by interaction with a mammalian homolog of the yeast global regulator RPD3

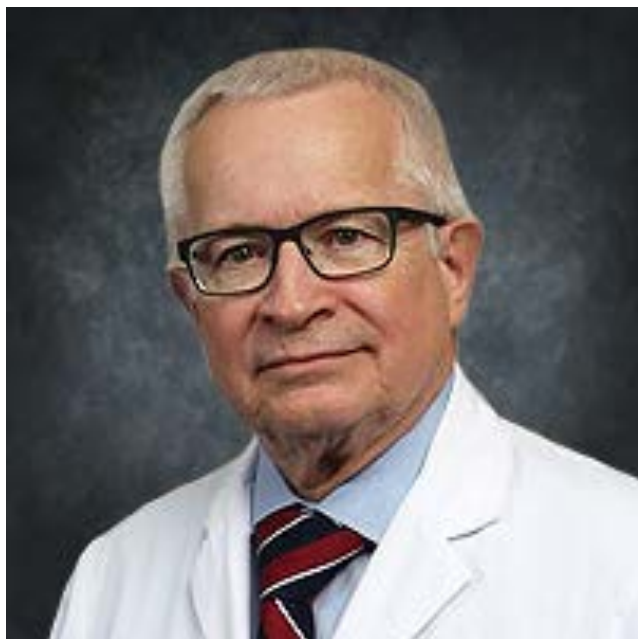
(transcription factor/corepressor/protein-protein interaction)

WEN-MING YANG, CARLA INOUE, YINGYING ZENG, DAVID BEARSS, AND EDWARD SETO*



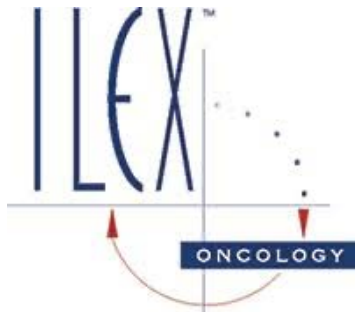
My Post-Doctoral Fellowship at the Institute for Drug Development at the CTRC

Daniel Von Hoff, MD, FACP



- Dan was involved in the beginning of the development of many FDA approved agents we now use routinely, including: mitoxantrone, fludarabine, paclitaxel, docetaxel, gemcitabine, irinotecan, nelarabine, capecitabine, lapatinib, vismodegib, nab-paclitaxel, nal-IRI, pexidartinib and many others.
- His clinical trial work has led to the approval of 3 of the 4 drugs approved by the FDA for treatment of patients with advanced pancreatic cancer.
- In total he has participated in more than 500 Phase I clinical trials

My First Industry Experience: Ilex Oncology



Lessons Learned at the CTRC

- Find a great mentor and learn all you can
- Forge relationships with smart people



Mace Rothenberg



Skip Burris



Tony Tolcher



Manny Hildago



Gail Eckhart



Eric Rowinsky



Lillian Su



SunYoung Ra



Sunil Sharma



Eric Raymond



Johann de Bono



Steve Weitman

Special Lecture

There Are No Bad Anticancer Agents, Only Bad Clinical Trial Designs—Twenty-first Richard and Hinda Rosenthal Foundation Award Lecture¹

Daniel D. Von Hoff^{2,3}

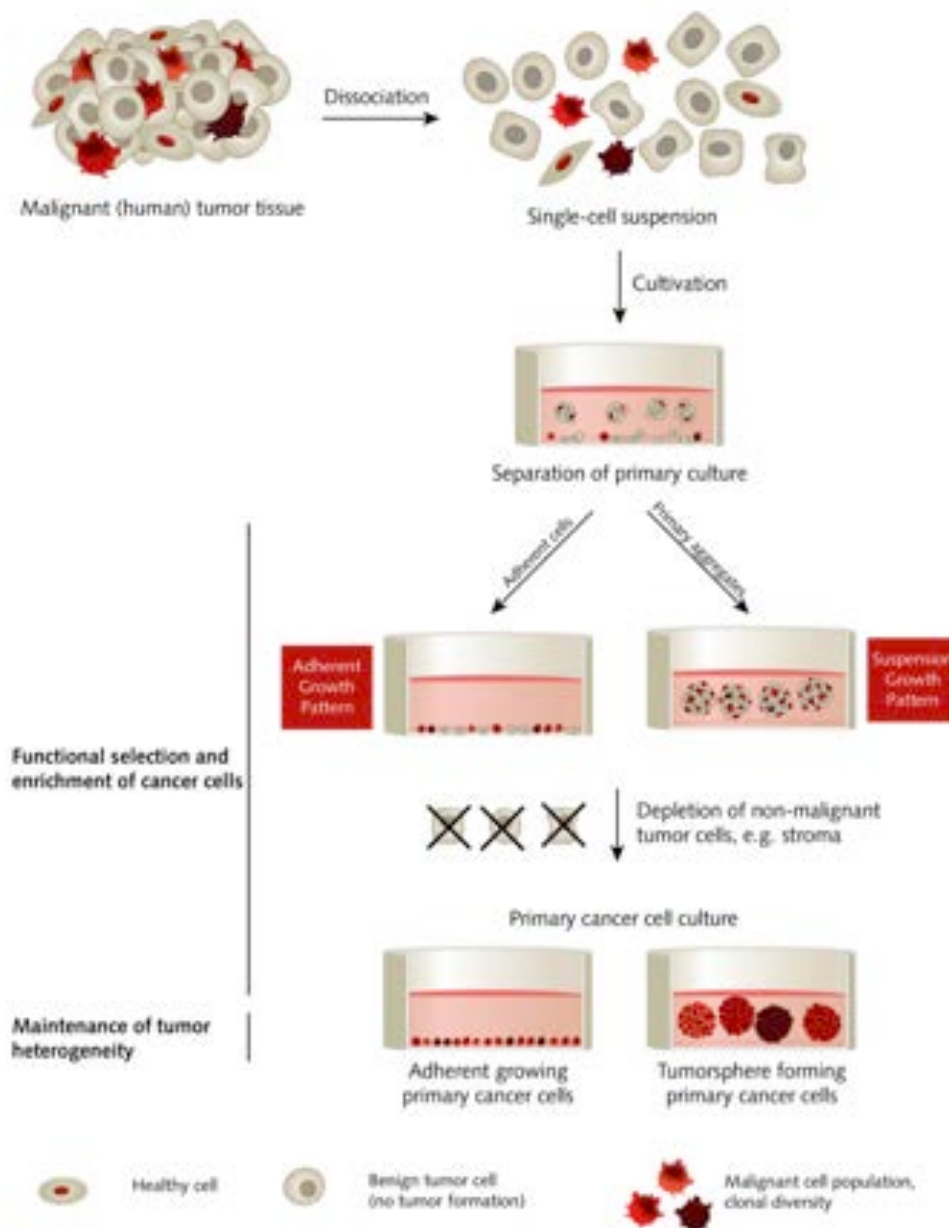
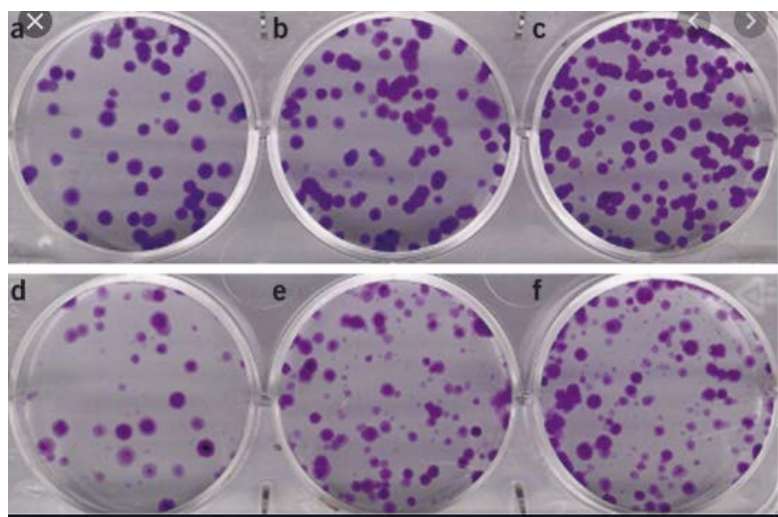
Institute for Drug Development, Cancer Therapy and Research Center, and Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78245

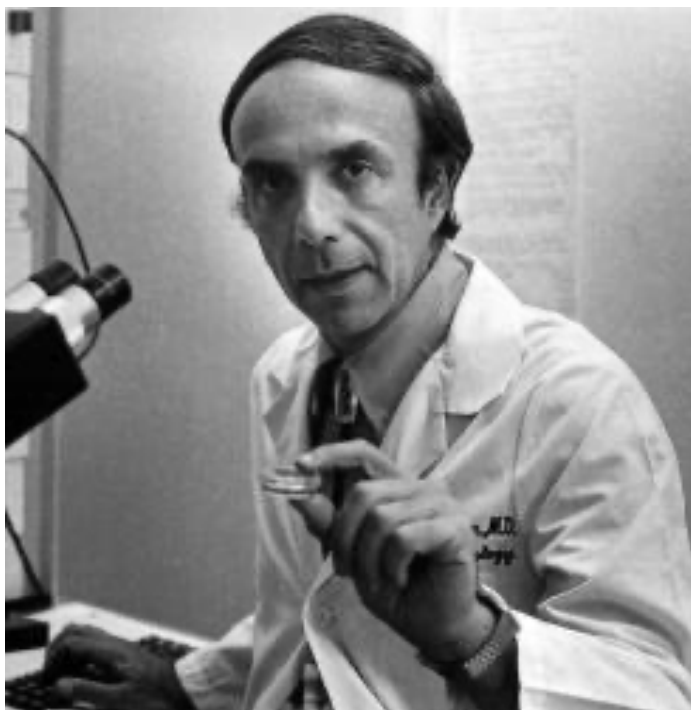
pointingly low. Fig. 1 details the number of new agents into clinical trials from 1975 to 1994 and the number agents eventually approved for clinical use. Overall, the 280 new agents brought into Phase I (dose-finding) trials in patients. Only 29 of them (10%) were eventu



Cancer Never Sleeps and Neither Should We

Utilization of Soft Agar Colony Formation Assay to Personalize Cancer Therapy

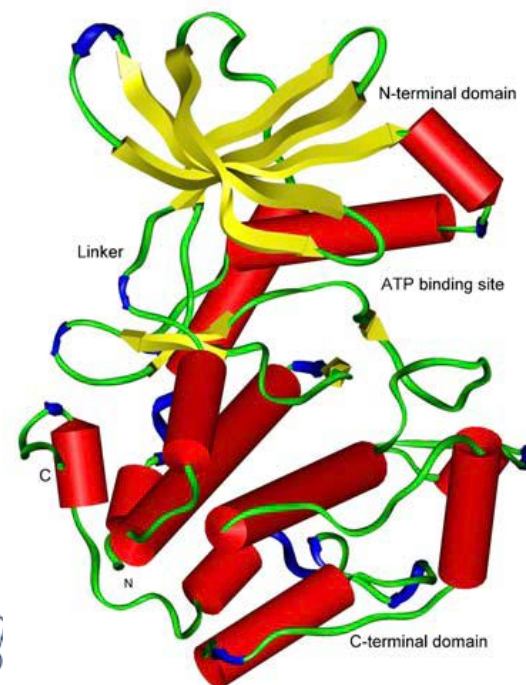
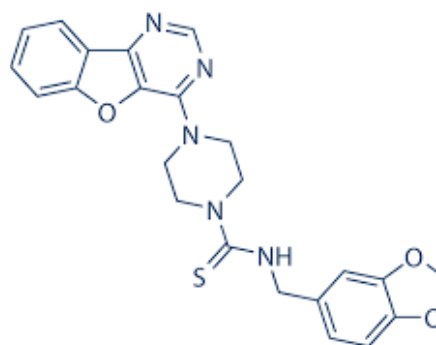
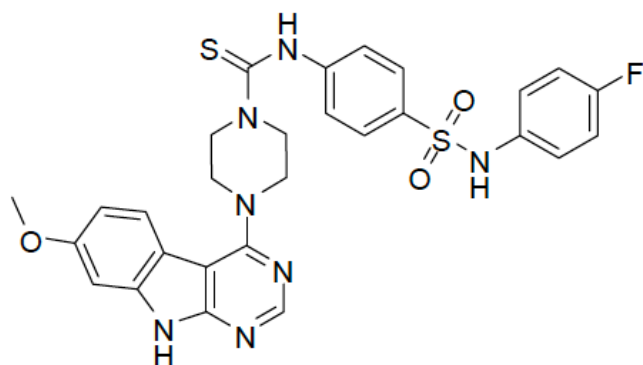
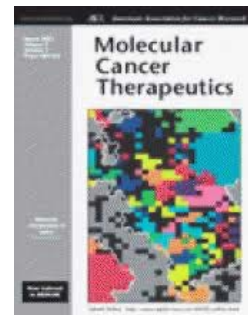




 **THE UNIVERSITY OF ARIZONA**
CANCER CENTER
A National Cancer Institute-designated Comprehensive Cancer Center



My Move to Arizona and Our Drug Discovery Team



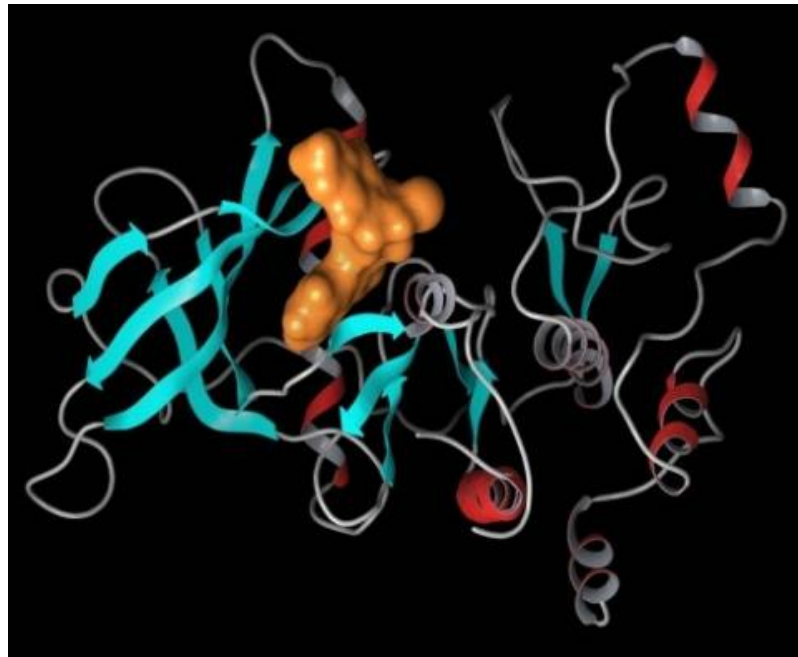
- There are three types of start up companies:
 - The spin-out company - Formed by a PI at a University and becomes an extension of their lab
 - The VC-formed company - VCs take your idea and form a company around it, fund it, control it, and make sure it succeeds
 - The true entrepreneurial company - You are the only one that believes in what you are doing and sacrifice everything you have to make it successful





- Founded July, 2003
- Product-focused drug discovery / development company.
- **IND filing anticipated in 2005**
- Pipeline with excellent pre-clinical activity.
- Novel drug discovery / development engine.
- \$5.2MM Series A

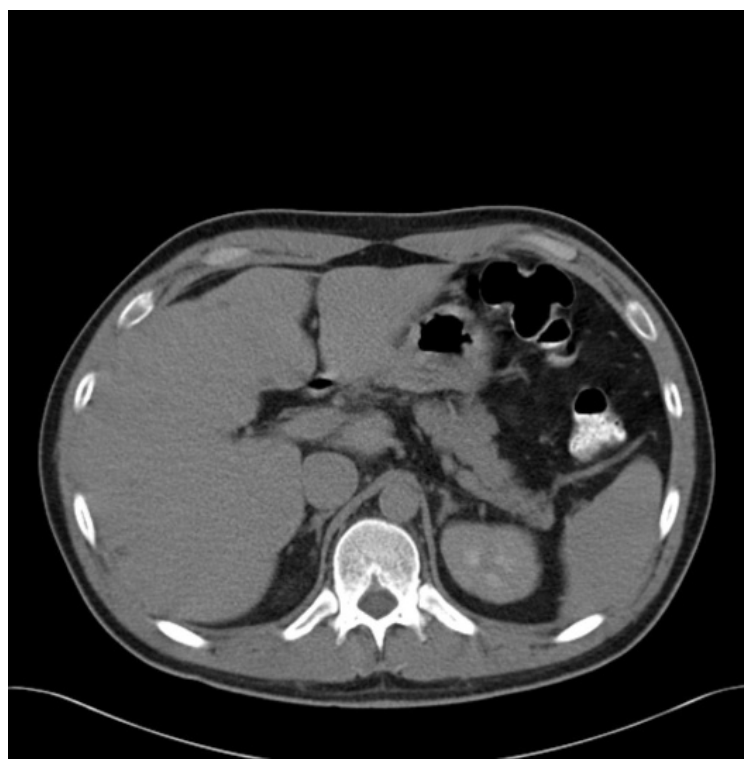
- Orally bioavailable
 - Suppresses DNA repair through Rad51, improves activity of many DNA-damaging therapies
 - Radiation, platinum agents, taxanes, and topoisomerase I and II inhibitors
- Activity (xenograft) as single agent and in combination
- Benign preclinical toxicity profile
- Pharmacological profile suggests broad clinical potential



- 24 y/o male with neuroendocrine tumor (small cell histology) with pronounced liver metastasis
- Prior lines of therapies
 - Cisplatin / etoposide (4 cycles) - SD
 - Topotecan (2 cycles) - PD
- Enrolled into SGI-0470-02 on Jan 22, 2008
 - Carboplatin AUC 6 mg•min/mL + paclitaxel 200 mg/m² + MP-470 100 mg
 - PR, Completed Cycle 7, then PD



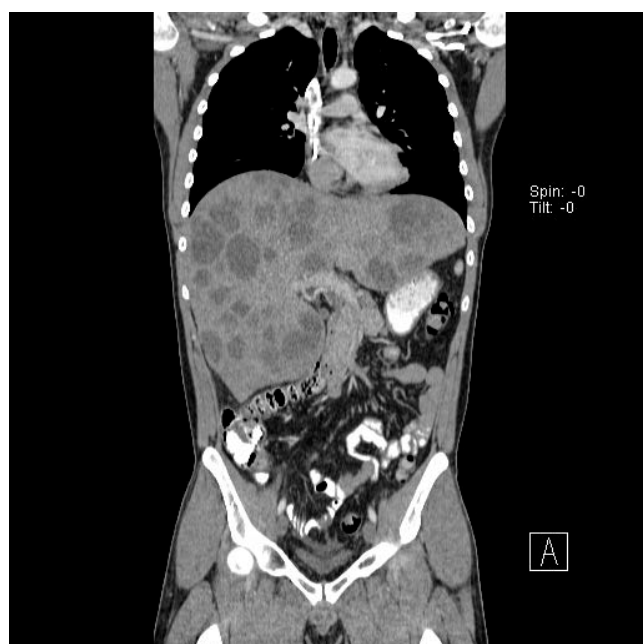
Baseline



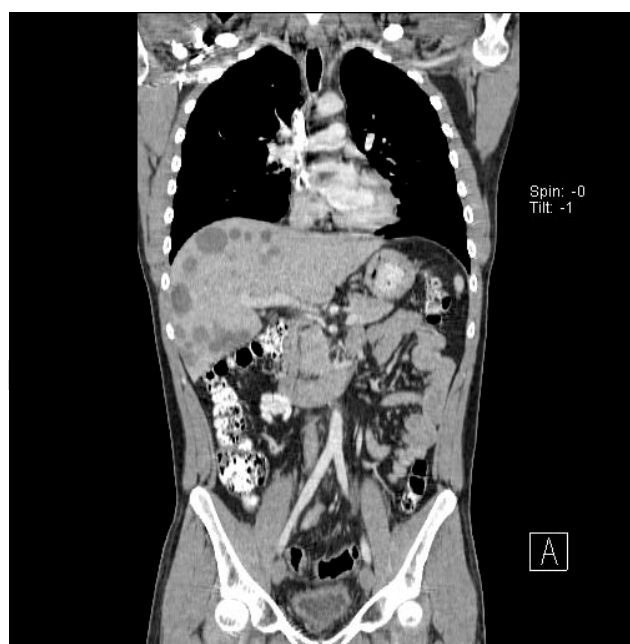
Cycle 6

Patient received 7 cycles of carboplatin/paclitaxel with MP-470 100 mg/day. Off study after Cycle 7.

Baseline



Cycle 2



Cycle 6



RECIST 240
% ↓ from BL --

168
30%

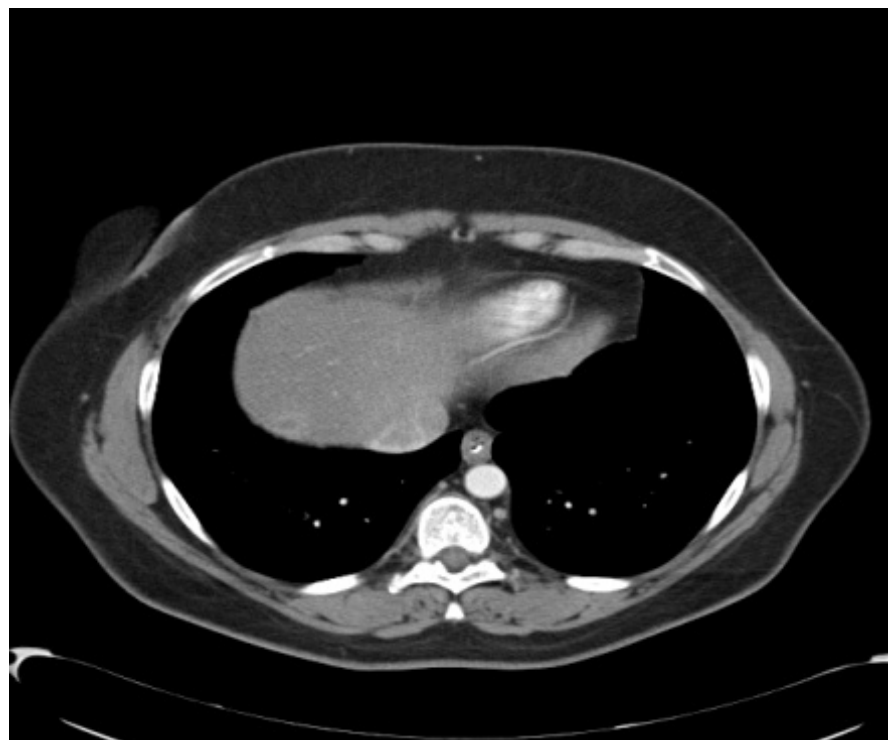
40
86%

- 41-yo female with neuroendocrine tumor with extensive liver mets
- Prior lines of therapies
 - Cisplatin / Etoposide x 4 cycles (SD)
 - Paclitaxel + XRT
 - Cyclophosphamide/ Bleomycin/ Vincristine/ Doxorubicin (CBVD)
- Enrolled in SGI-0470-02 and received carboplatin / etoposide + MP-470 200 mg/day



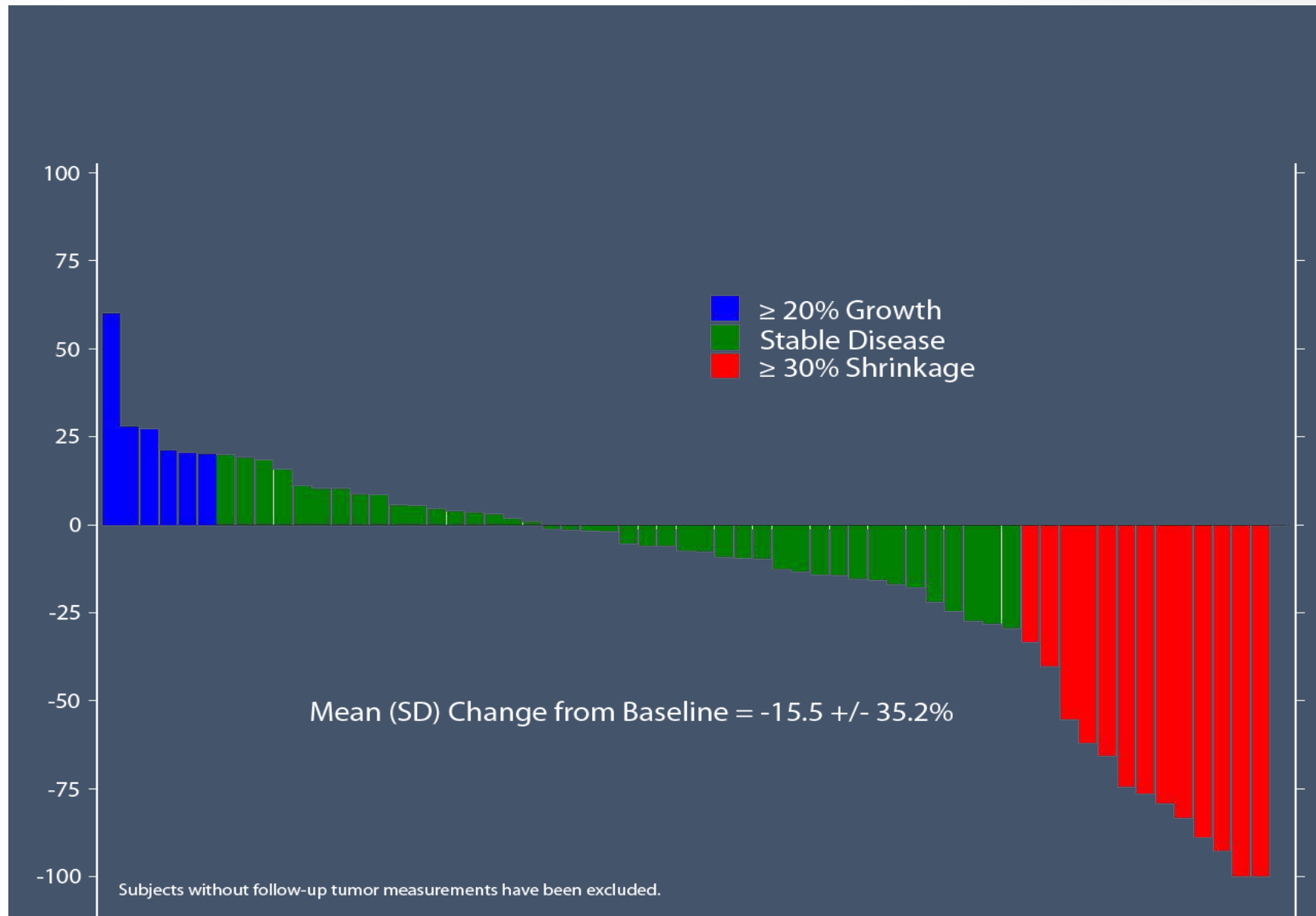
RECIST:

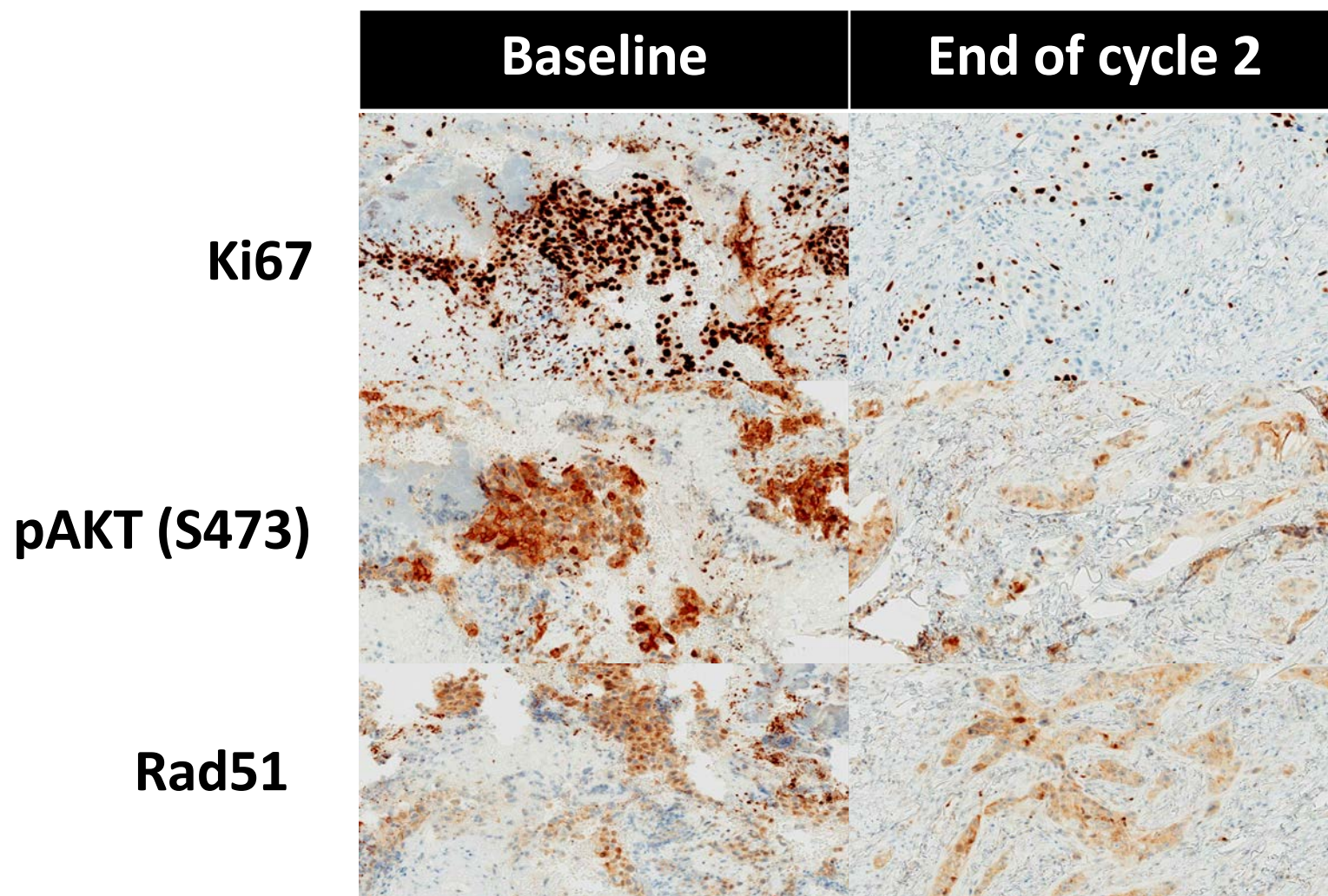
BL = 96



Cycle 6 = 20

Waterfall Plot of Best Responses





Montigen Pharmaceuticals Was Acquired by SuperGen in 2006



 **Deseret News**

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BUSINESS

SuperGen agrees to acquire Montigen Pharmaceuticals

By Deseret News | Jan 28, 2006, 12:00am MST



Dublin, California

Development	Preclinical	Phase 1	Phase 2	Phase 3	Approved	Marketed
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Dacogen® (decitabine) for Injection MGI PHARMA in N. America, JNJ Rest of World

Nipent® (pentostatin for injection) Hospira, Inc.

MP470 TK Inhibitor

Signal Transduction & DNA Repair Prevention – GBM, NSCLC, SCLC, GIST

MP529 Aurora-A Inhibitor

Mitotic Failure Induction – Pancreatic, Colorectal, Breast, Prostate

S110 DNMT1 Inhibitor

DNA Hypomethylation – MDS, AML, Solid Tumors

PIM

Potent Apoptosis Induction - Lymphomas, AML, Prostate

JAK2

Cytokine Signal Inhibition – Myeloproliferative Disorders, Solid Tumors

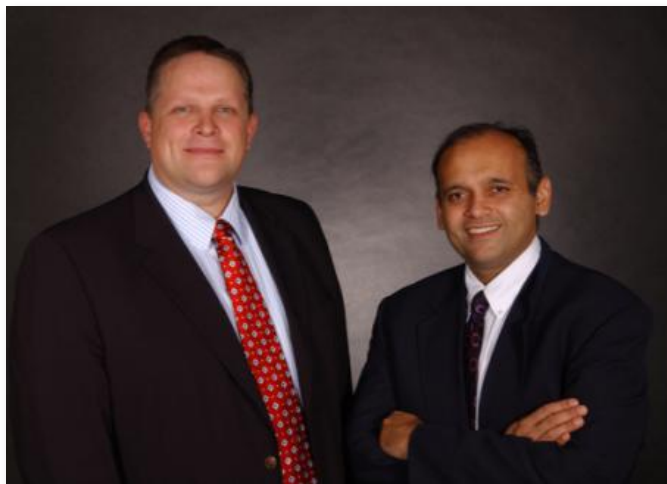
- FDA Approved Indication: Myelodysplastic Syndrome (MDS)
 - Broad Label - All FAB Classifications
 - IPSS (Int-1, Int-2 & High Risk)
 - *De novo* & secondary MDS
- Additional Development
 - MDS Survival Phase III EORTC trial 1H 2008
 - JNJ Guided to EMEA submission in 2008
 - Elderly AML Phase III ongoing
- Licensed to MGI Pharma Worldwide
 - \$23.75M Milestone Payments Outstanding
 - 20% – 30% royalty on all worldwide sales
 - Sublicensed to JNJ outside of North America
 - Eisai to acquire MGI Pharma Q1 08


DACOGENTM
decitabine for injection

I NEVER Imagined Doing Some of the Things I Have Done



- Novel initiative to strengthen early-phase clinical trials as well as drug discovery efforts at HCI
- Preclinical and Clinical components
- Center Leadership:
 - Director: Sunil Sharma, MD, FACP
 - Co-Director: David Bearss, PhD

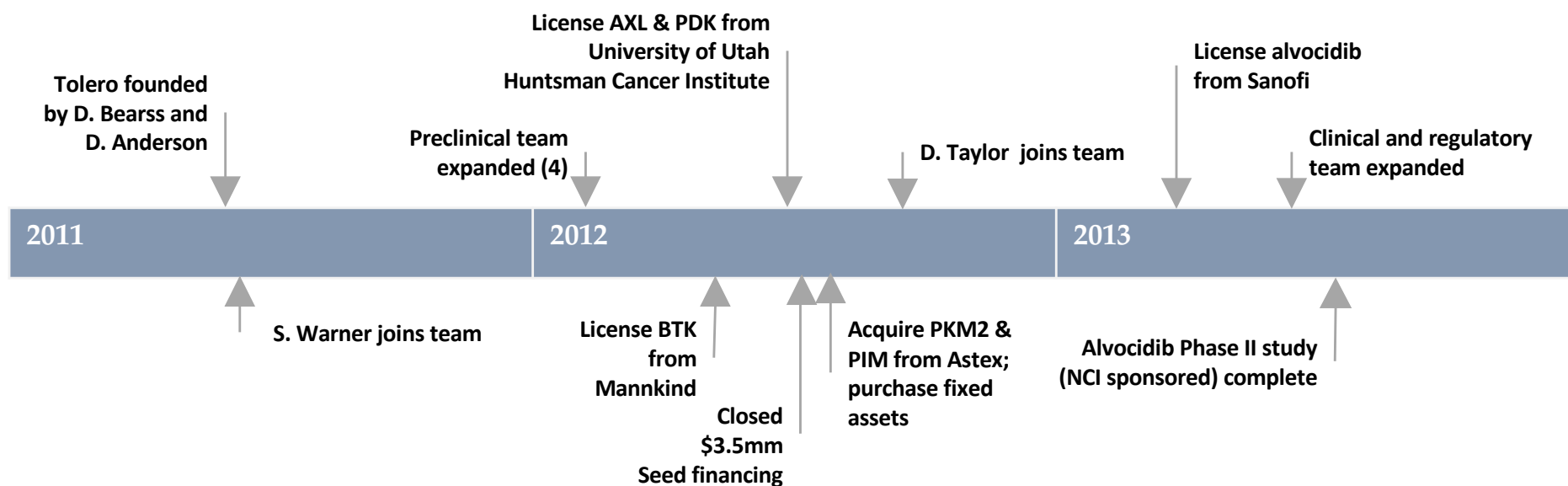


Program	Collaborative Project 
Nuclear Control: Nuclear Oncogenes	Targeting ETS in sarcoma and prostate cancer
Cell Response: Breast cancer	Mouse models and microarray signatures for Axl kinase inhibitors
Nuclear Control: Epigenetics Gastrointestinal Cancers: Stem Cell Targeting	Development of inhibitors of demethylase and mutant APC
Imaging, Diagnostics, and Therapeutics	Preclinical and IIT studies for BCL-2 targeting in synovial sarcoma Targeting NEK2 for therapy in multiple myeloma and other tumors
Clinical Research	Six Phase I trials with novel agents: Inhibitors of HDAC, Activin-like kinase 1, and Aurora kinase; Novel liposomal platinum, Novel anthracycline, Novel CD38 antibody

Tolero Pharmaceuticals: Company Early History



TOLERO
PHARMACEUTICALS





- When a door opens, go through it even when you don't know what is on the other side
- It's a lot harder than you think to get funding, even when you have a clinical asset with a lot of clinical data (VCs will always find something wrong with what you are doing)
- Just because a Big Pharma company couldn't make it work doesn't mean it doesn't work... Remember, there are no bad drugs, just bad clinical trials

Alvocidib Monotherapy Demonstrates Reproducible Responses in Relapsed / Refractory CLL

Phase I and II trials utilizing a hybrid dosing schedule (30-min loading dose followed by 4-hr infusion) shows alvocidib efficacy in CLL

	OSU0055 ¹ (N = 52)	OSU0491 ² (N = 64)	Sanofi EFC6663 (N = 165)
Overall response	21 (40%)	34 (53%)	50 (30%)
Complete response (CR)	-	1 (2%)	6 (3%)
Partial response (+ nPR)	21 (40%)	33 (51%)	44 (27%)

1. Single center Phase I dose-escalation trial in B-CLL/SLL
2. Single center Phase II trial in genetically high-risk CLL

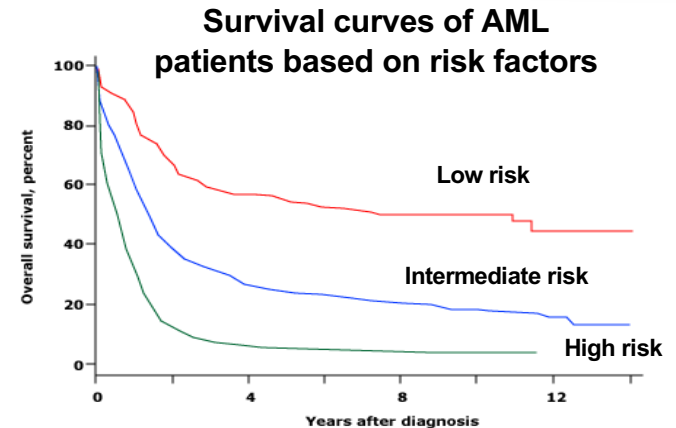
Clinical Experience with Alvocidib in CLL Patients Has Decreased Adverse Events

Study	Incidence of Tumor Lysis Syndrome	Grade \geq 3	Patients Needing Dialysis	TLS-related Deaths
OSU0055 n=52 (4-week schedule)	55%	12%	14%	6%
OSU0491 n=64 (4- and 3-week schedules)	44%	42% (4-wk) 22% (3-wk)	5%	0%
Sanofi EFC6663 n=165 (4-week schedule)	13%	12%	8%	1%

- Safety protocol implemented to reduce incidents of adverse events
- TLS (\geq Grade 3) in AML studies currently 5%



Judith E. Karp, MD
Professor of Oncology and Medicine
Director, Leukemia Program
The Sidney Kimmel Comprehensive Cancer Center at Johns
Hopkins Hospital
Baltimore, MD



- Current standard of care (known as 7+3) is ara-C (cytarabine) and daunorubicin
- Majority of AML patients have high-risk features (75%)¹
 - 55 years of age or older, 62% of diagnosed AML patients
 - Deletions in chromosomes 5 and 7, each of which occurs in 30% of AML patients
 - Secondary AML (AML related to prior chemotherapy treatments)
- Standard of care in AML leads to significant morbidity and treatment-related mortality in up to 20% of patients¹
- Patients that achieve a complete remission (CR) may be eligible to undergo a bone marrow transplant (BMT), considered to be the only curative treatment for AML

- The National Cancer Institute originally developed Alvocidib (Drs. Sausville, Grever, and Byrd)
- Tolero negotiated an exclusive worldwide license from Sanofi in 2013
- Alvocidib is a potent pan-CDK inhibitor
 - Significant activity across 400 patients
 - Considered to be a profoundly cytoreductive novel cancer agent
- Most recent clinical trial in front line AML
 - 70% CR rate for induction therapy, as compared to 46% for standard of care: Ara-C + daunorubicin (“7+3”)
 - Sub-group analysis reveals up to a 96% CR rate at induction
- Alvocidib represents the potential for a true advance in overall and progression-free survival in first-line AML
- Further opportunities in combination with other agents
 - For example, Pharmacyclics’ ibrutinib in CLL
- Tolero has also engaged in extensive profiling of clinical samples from alvocidib-treated patients in an effort to improve patient selection

In intermediate- and high-risk patient populations, alvocidib in combination shows significant improvement over 7+3, the current AML standard of care.

NCI-8972 Final Results: % Complete Remission

Randomized Phase II Study 2:1 165 Patients

ACM (109 patients)

- Alvocidib: 50 mg/m² IV day 1-3
- Ara-C 2 g/m² IV over 72 hr, day 6-8
- Mitoxantrone 40 mg/m² IV day 9

7+3 (56 patients)

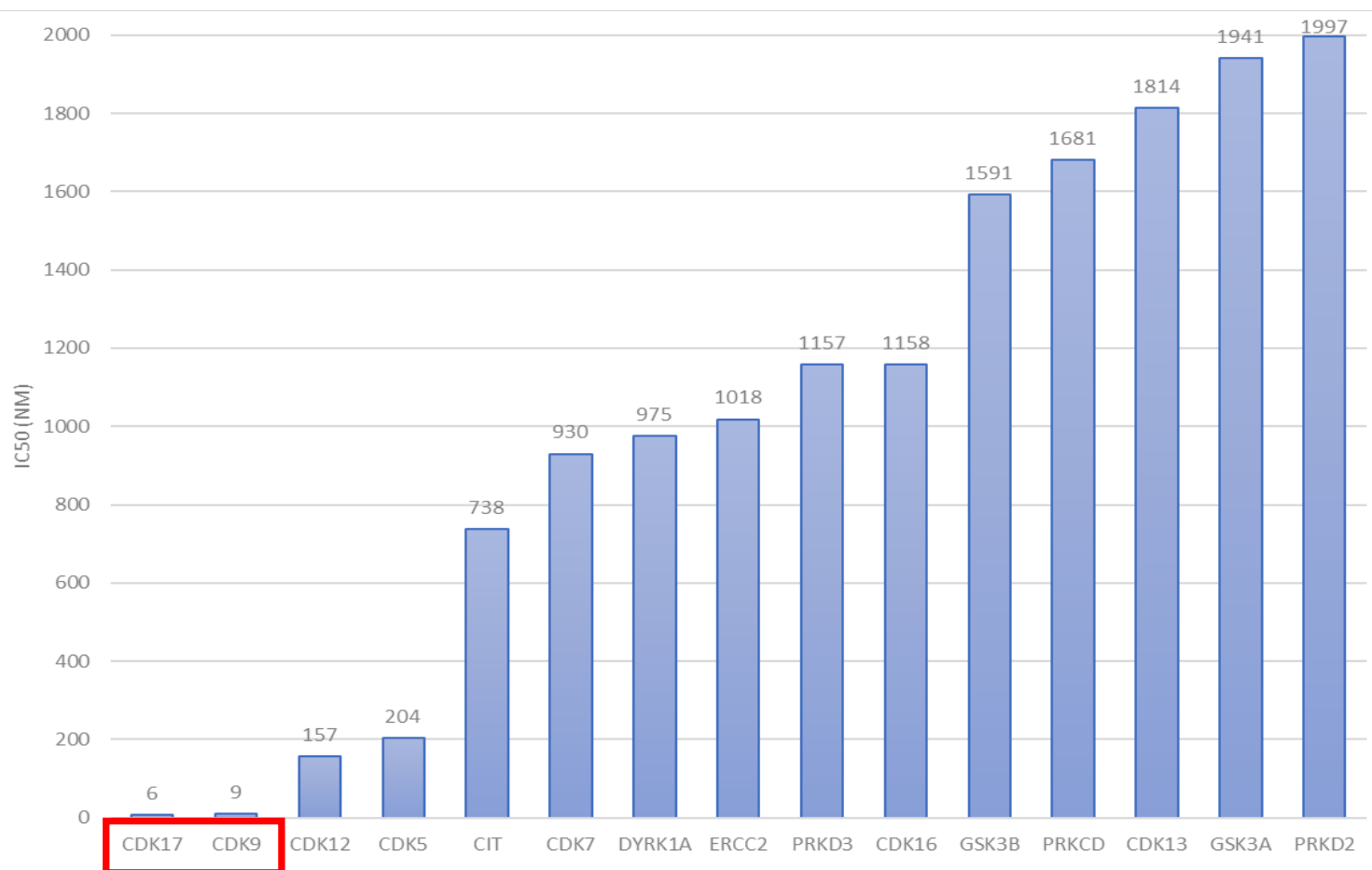
- Ara-C 100 mg/m²/day IV days 1-7
- Daunorubicin 90 mg/m² IV days 1-3

	<u>ACM</u>	<u>7+3</u>
Primary Endpoint: CR rate	70%	46%
<u>CR by Risk Factors:</u>		
No Adverse	25/25 (100%)	13/18 (72%)
Adverse Genetics	30/58 (52%)	10/27 (37%)
<i>Cytogenetics</i>	22/48 (46%)	6/21 (29%)
<i>Complex</i>	14/30 (47%)	3/16 (19%)
<i>Monosomal</i>	13/24 (54%)	3/12 (25%)
<i>FLT3 ITD+</i>	9/13 (69%)	3/6 (50%)
Secondary AML	31/52 (60%)	9/26 (35%)
>1 High-risk feature	51/84 (61%)	13/38 (34%)

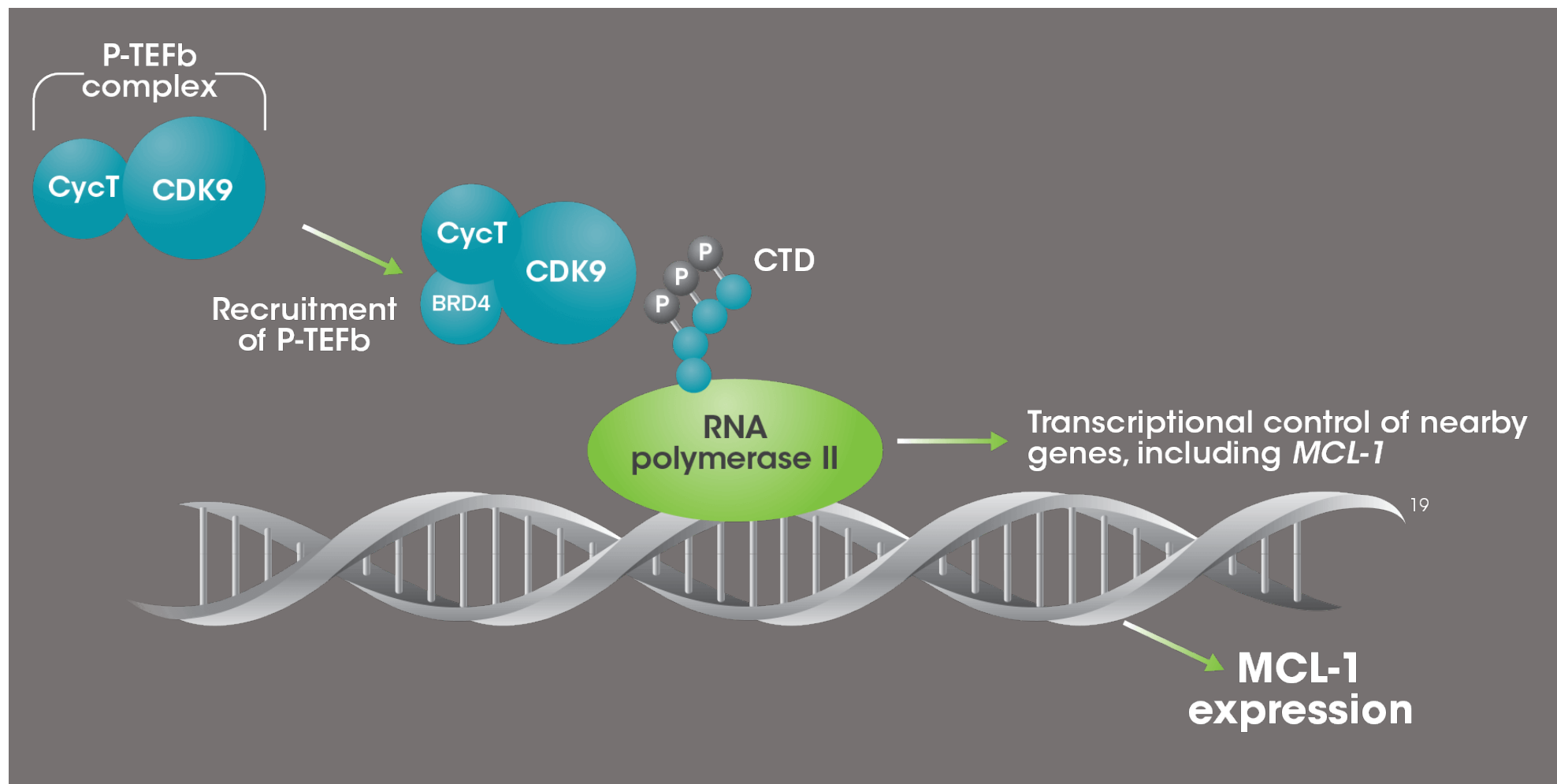
Randomized Phase II trial provides conclusive data to support further development

Kinases inhibited by alvocidib at cellular concentrations below 2 μ M

Methodology: Kinobeads (proteomics); Cell Lysate mixture: K-562, COLO 205, MV-4-11, SK-N-BE

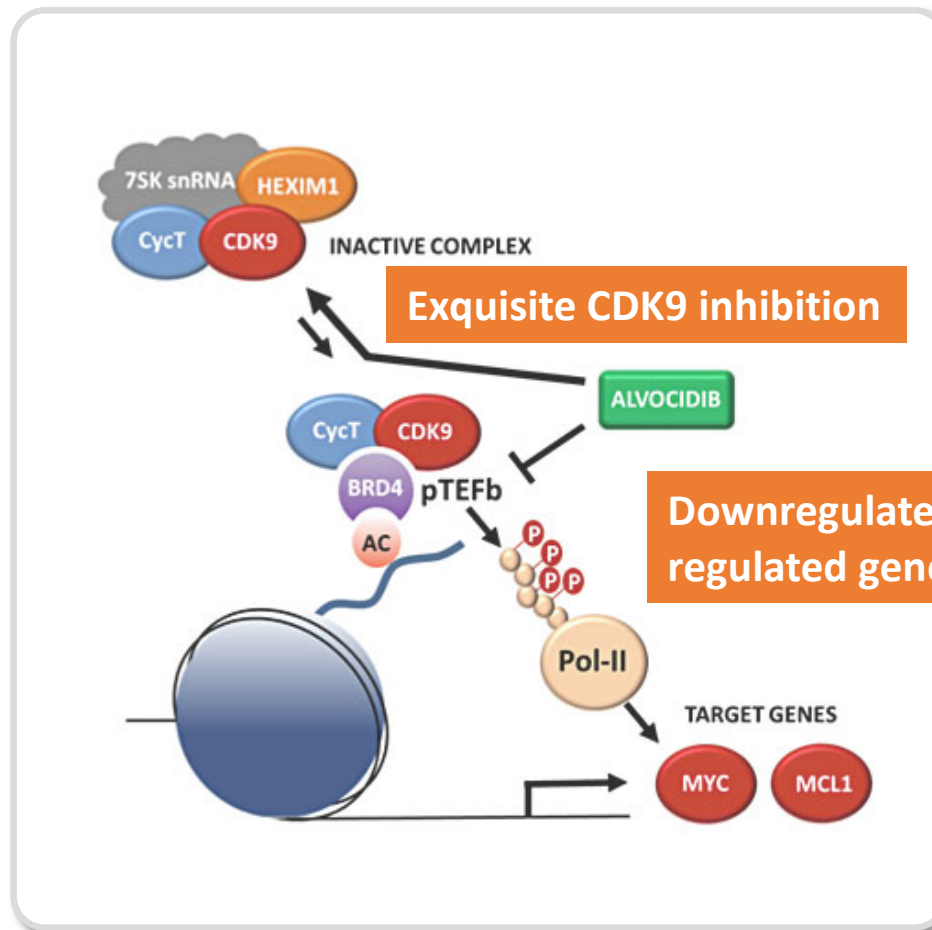


Klaeger S, et al. *Science*. 2017;358(6367)



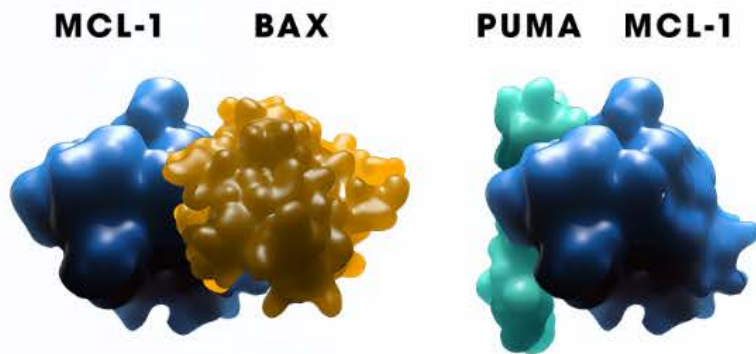
Boffo S, Damato A, Alfano L, Giordano A. CDK9 inhibitors in acute myeloid leukemia. *J Exp Clin Cancer Res.* 2018;37(1):36. 10.1186/s13046-018-0704-8.

Alvocidib Disrupts Super Enhancer Gene Expression



Oncotarget. 2014; 6(5); 2667-2679

Apoptosis Regulation



Directly binding
and sequestering
pro-apoptotic
proteins

Binding to
sensitizer
proteins



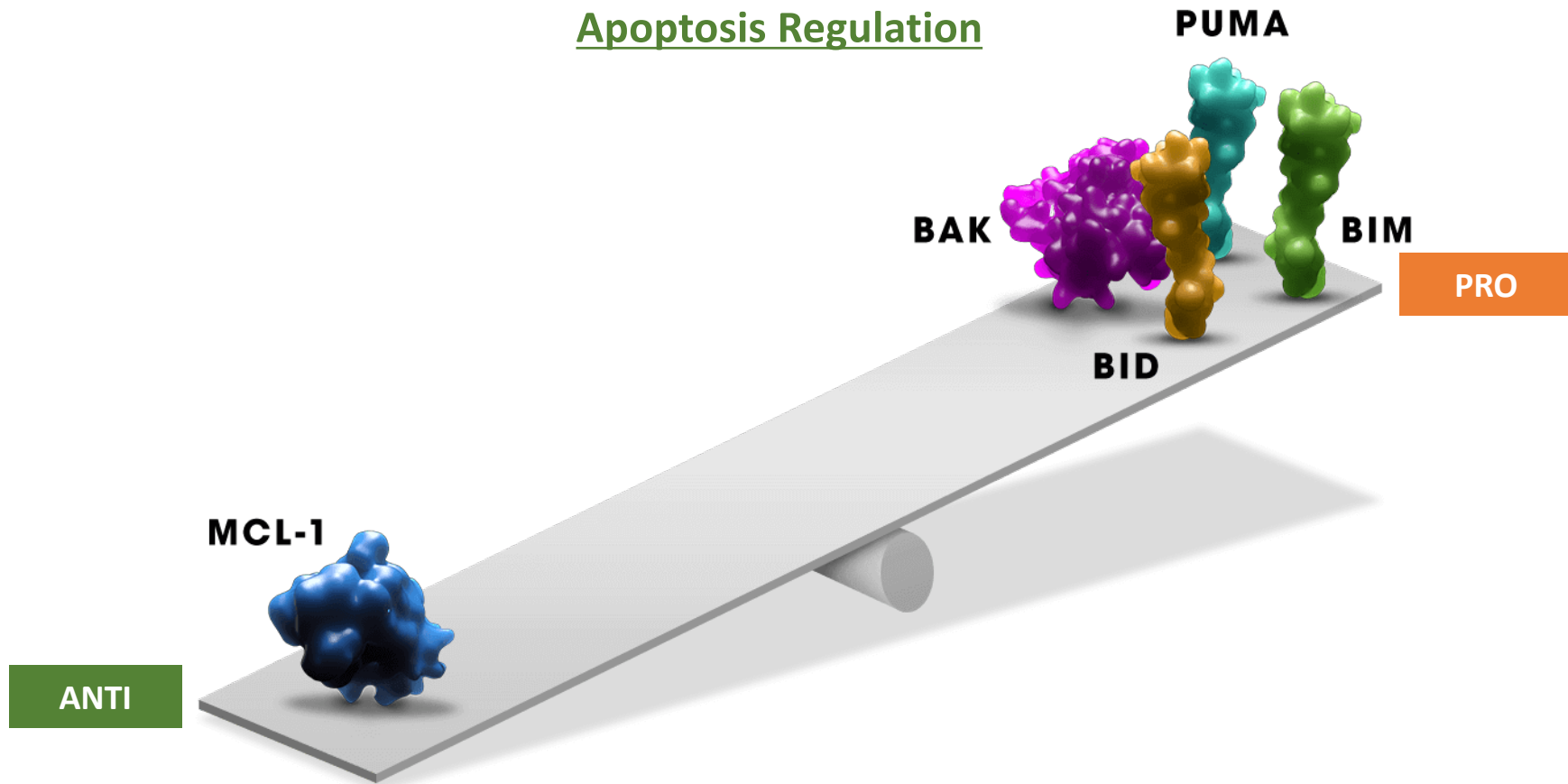
Mitochondrial Metabolism



- Promotes normal cristae structure as well as mitochondrial fusion
- Supports oxidative phosphorylation, ATP production, and maintenance of membrane potential

Perciavalle & Opferman *Trends Cell Biol.* 2013;23(1):22-29
Gores & Kaufmann *Genes Dev.* 2012;26(4):305-311

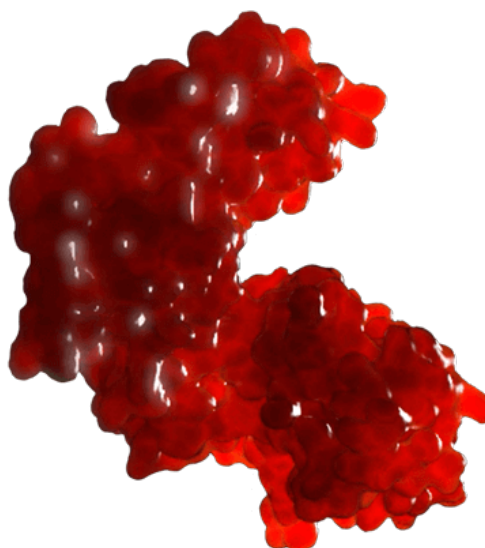
Apoptosis Regulation



Downregulating MCL-1 tips the balance to pro-apoptotic proteins

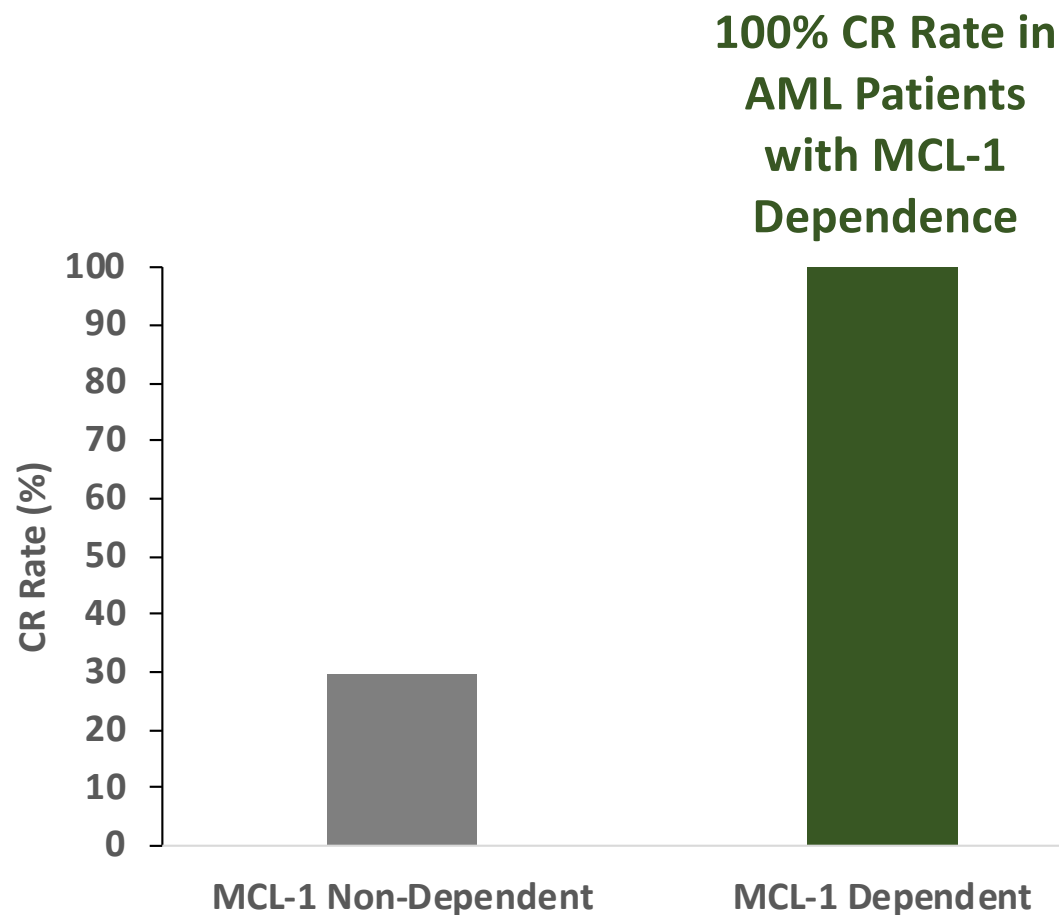
Del Galzo Moore VDG, Letai A. BH3 profiling--measuring integrated function of the mitochondrial apoptotic pathway to predict cell fate decisions. *Cancer Lett.* 2013;332(2):202-205.

CDK9



Cyclin-dependent kinase 9, or CDK9, is a crucial upstream regulator of MCL-1. CDK9-mediated transcription of MCL-1 may play an important role in the survival of cancer cells, as has been observed in AML and other hematologic malignancies. Inhibition of CDK9 results in rapid depletion of MCL-1, which may restore apoptosis in AML blasts.

Del Galzo Moore V & Letai A *Cancer Lett.* 2013;332(2):202-205
Boffo S *et al. J Exp Clin Cancer Res.* 2018;37(1):36. 10.1186/s13046-018-0704-8
Chen *et al. Blood.* 2005;106(7):2513-2519



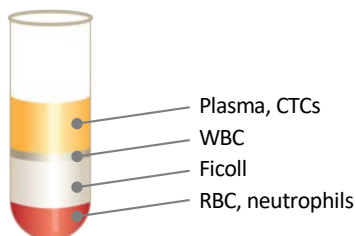
- Pre-treatment bone marrow from newly diagnosed AML patients tested for MCL-1 dependence by mitochondrial BH3 profiling
- MCL-1 dependence $\geq 40\%$ appeared to predict response to **ACM*** & **not 7+3****

*Alvociclib followed by Cytarabine & Mitoxantrone
**7+3 7 days cytarabine 3 days daunorubicin

Enrichment increases probability of success for alvocidib CDK9i studies

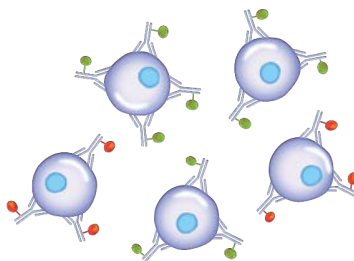
1

Leukocyte Isolation
Cells are separated by Ficoll gradient



2

Leukocytes are stained for blast cell population



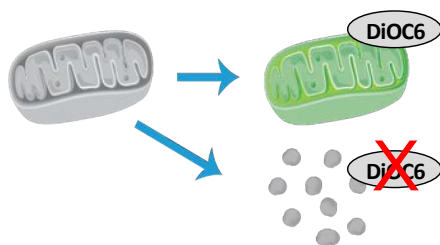
3

Cell perturbation with T-MS1 NOXA mimetic peptide (H₂O and CCCP as controls)
Cells dependent upon MCL-1 will apoptose



4

Cells with intact mitochondria (not apoptosed) will stain with DiOC6



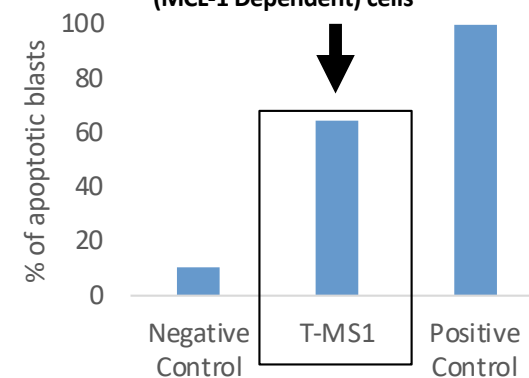
5

Detect apoptotic blast population by flow cytometry



6

Quantification of apoptotic (MCL-1 Dependent) cells



MCL-1 Dependent Relapsed/Refractory Acute Myeloid Leukemia (AML) patients (n=47)

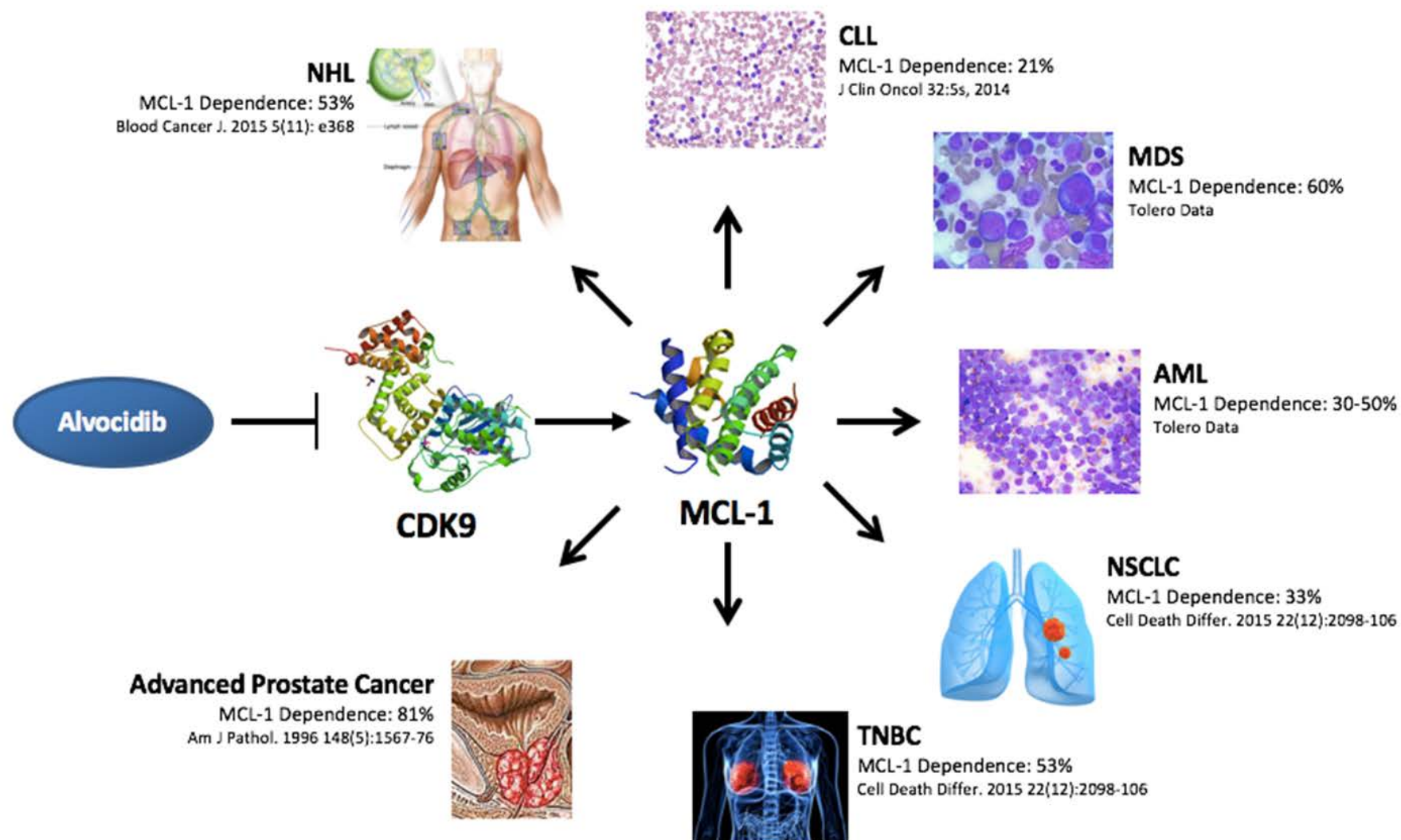
Response Characteristic	CR+CRi (%)	CR+CRi - Evaluable for Response (%)
Overall	13/23 (57%)	13/19 (68%)
Refractory	7/12 (58%)	7/11 (64%)
Early Relapse	4/7 (57%)	4/5 (80%)
Late Relapse	2/4 (50%)	2/3 (67%)
Unfavorable cytogenetics	2/5 (40%)	2/4 (50%)

Stage 1 met criteria of CR rate to proceed to Stage 2

- CR: n=10, CRi: n=3; ORR = 61% (1 patient achieved PR)
- 10 (43%) patients proceeded to allogeneic stem cell transplant
- Median OS = 11.2 months (95% CI [3.0, 16.8])
- 4 early deaths before response assessment

- CDK9 phosphorylates RNA polymerase and controls the transcription of key proteins involved in cancer such as c-Myc and MCL-1
- In normal cells, MCL-1 activity is controlled through its interactions with NOXA, a selective antagonist of MCL-1
- Cancer cells may develop a dependency on MCL-1. By targeting CDK9, it may be possible to exploit MCL-1 dependence by blocking the expression of MCL-1
- MCL-1 is a member of the BCL-2 family of proteins and is commonly over-expressed in myeloid leukemia and MDS
- Many heme malignancies depend on MCL-1 to avoid apoptosis

Alvocidib Targeting MCL-1 Dependence: Indication Expansion



Japanese pharma snaps up cancer biotech Tolero



Fotolia

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Dive Brief:

- Japanese pharma Sumitomo Dainippon Pharma has picked up oncology and hematology biotech Tolero Pharmaceuticals for up to \$780 million.

The Tolero Team



Tolero is committed to developing meaningful medicines to improve and extend the lives of patients with serious diseases.



- Product pipeline targets important biological drivers of severe diseases, such as acute and chronic leukemias, anemia, and solid tumors
- By targeting the molecular basis of these diseases, we are able to leverage companion diagnostics and biomarkers to expand intellectual property, accelerate development, and improve patient outcomes
- Tolero is part of the Sumitomo Dainippon Pharma Global Oncology Team
 - GOO/DCI/OCU (Osaka and Tokyo)
 - BBI (Boston)
 - Tolero (Utah)

"Good Science Is Good Medicine, and Good Medicine Is Good Business"

- **Lead program, alvocidib, is a late-stage CDK9 inhibitor with a novel biomarker-based approach to hematological cancers**
 - CDK9 regulates the transcription of proteins involved with cancer, including MCL-1
 - Significant clinical experience in over 400 patients
 - Potential to improve patient outcomes in AML
 - Additional opportunities in MDS, MM, and solid tumors
- **Innovative early-stage pipeline including:**
 - TP-0903 (AXL kinase inhibitor)
 - TP-0184 (ACVR inhibitor)
 - TP-1287 (Oral CDK9 Inhibitor)
 - TP-3654 (Pim Kinase Inhibitor)
 - TP-1454 (PKM2 Activator)
 - TP-5809 (TNK1 Inhibitor)

- The preeminence of science is the bedrock of successful biotech corporate cultures
- Making drugs is hard, but it's far more compelling to me than making apps and gadgets
- We are making innovative medicines aimed at dramatically improving patients' lives by bringing discoveries from the bench to the bedside
- This science-based mission is a bold and important one for the company, and for society
- If creativity and passion are forced to “fit” a conventional corporate mold and science isn't respected, we will fail
- Reproducible, high-quality science and the objectivity of the scientific method are cornerstones of long-term success
- As Agios CEO David Schenkein has said, R&D is truly the beating heart of biotech

My Proudest Achievement- The Bearss Family



Thank You!