

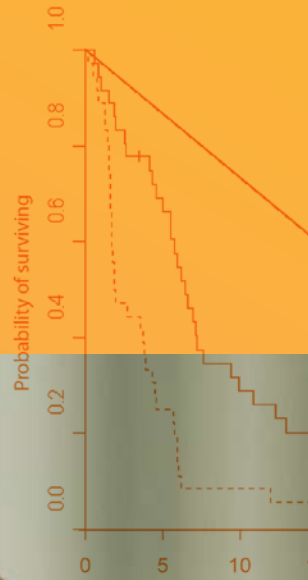
Upper left:
Mark E. Davis, Ph.D.,
Warren and Katharine Schlinger
Professor of Chemical Engineering,
California Institute of Technology

Center:
Human dose vial of ribonucleotide
reductase inhibitor used in the first
clinical trial.

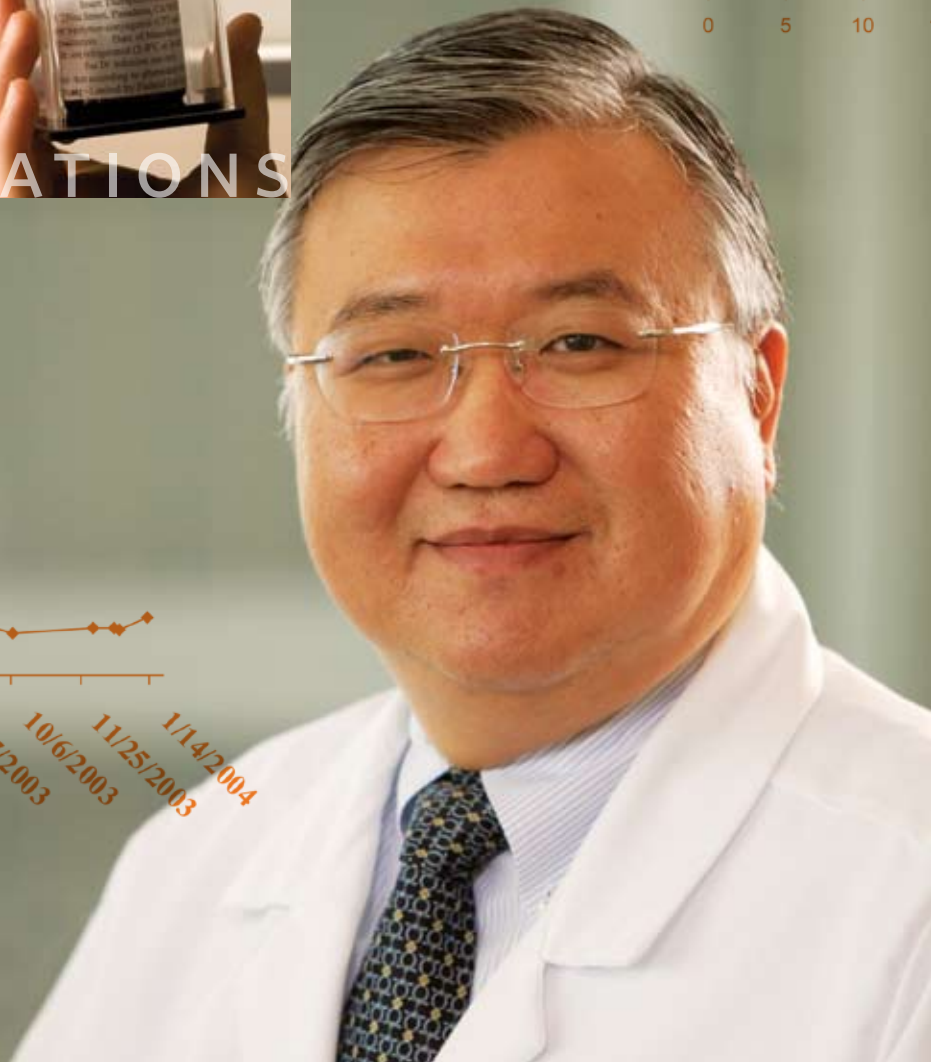
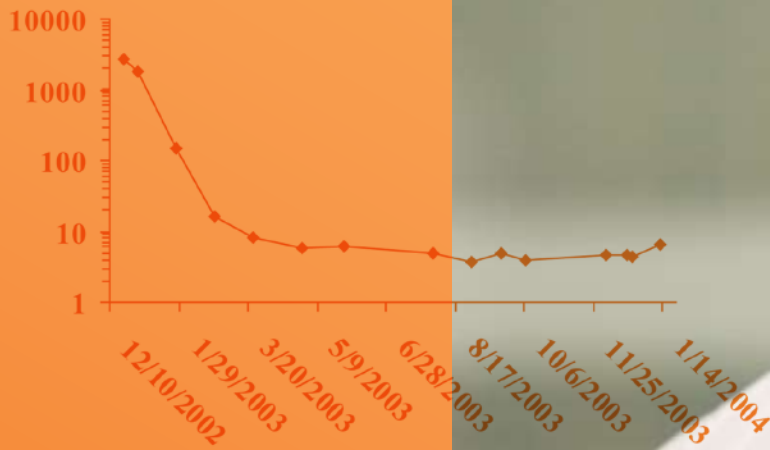
Lower right:
Yun Yen, M.D., Ph.D., City of Hope



Photo courtesy of California Institute of Technology



COLLABORATIONS



DEFEATING DRUG RESISTANCE

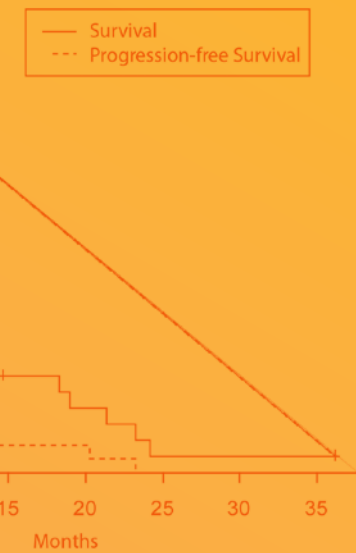
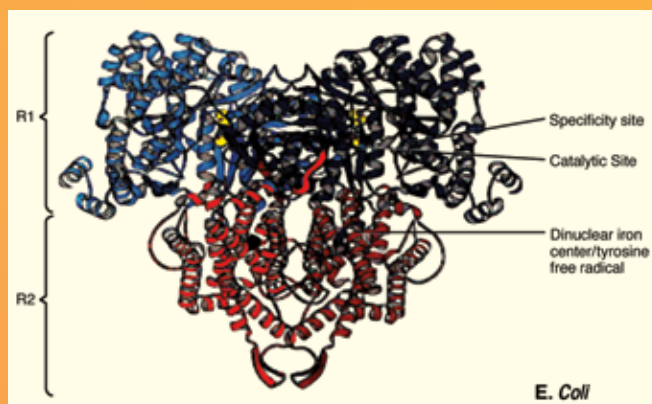
RIBONUCLEOTIDE REDUCTASE INHIBITORS

Many cancer drugs seem to work well at first. But too often, the disease returns. And when it does, it can hit even harder and faster than before. Many cancers actually develop resistance to chemotherapy. Finding a way to defeat this drug resistance is a significant step toward finding a cure.

At City of Hope, Yun Yen, M.D., Ph.D., director of Clinical and Molecular Pharmacology and co-leader of the Developmental Cancer Therapeutics Program, believes the answer may be found in an enzyme that cells use naturally to repair and restore themselves. The enzyme ribonucleotide reductase (RR) converts ribonucleotides into the building blocks of DNA, an essential part of the normal process of cell growth, including the ability to fix damaged genes. But in cancer cells, RR production can go into overdrive, allowing cancers to survive attacks by chemotherapy and promoting the spread of new malignant cells that can invade healthy tissues.

For 17 years, Yen's research has focused on understanding the gene that codes for RR and how the enzyme itself helps cancer spread. One well-known chemotherapy drug, hydroxyurea, is known to work by inhibiting RR. But if surviving cancer cells learn to resist the drug, it can lead to recurrence. Today, Yen's group is

pressing to find more effective anticancer agents, including combining newer RR inhibitors with gemcitabine, the only drug approved for pancreatic cancer.



Yen discovered the mechanism by which cancer cells become resistant to gemcitabine — a finding that is actively being exploited in the search for new cancer drugs.

Collaborative research is accelerating progress in overcoming drug resistance. Within City of Hope, David Horne, Ph.D., director of the Synthetic Chemistry Core Facility, and Yate-Ching Yuan, Ph.D., manager of the Biomedical Informatics Core Facility, are designing new compounds with the ability to inhibit RR. These are tested at City of Hope's High Throughput Screening Core, directed by M.L. Richard Yip, Ph.D. The core facility is a resource where newly synthesized chemicals and thousands more from a library of molecules can be screened rapidly to assess whether they hold potential as possible treatments.

Meanwhile, Yen is also working with John Rossi, Ph.D., Lidow Family Research Chair in the Division of Molecular Biology, to investigate the use of small interfering RNA (siRNA) to “silence” the genes that produce RR through a mechanism called RNA interference (RNAi). Rossi is using the RNAi approach to fight HIV, and this approach is one of the most promising new investigational

Scientists at City of Hope and Caltech are collaborating to develop nanoparticles that can deliver drugs directly to cancer cells.

therapies for many diseases. The 2006 Nobel Prize in Medicine was awarded for the discovery of the RNAi mechanism.

Taking the siRNA strategy a step further — to a level reminiscent of science fiction — City of Hope researchers are pursuing an inter-institutional project with Mark E. Davis, Ph.D., Warren and Katharine Schlinger Professor of Chemical Engineering at the California Institute of Technology, and a local start-up company called Calando Pharmaceuticals. Davis has engineered nanoparticles made of polymers that can deliver drugs directly to cancer cells.

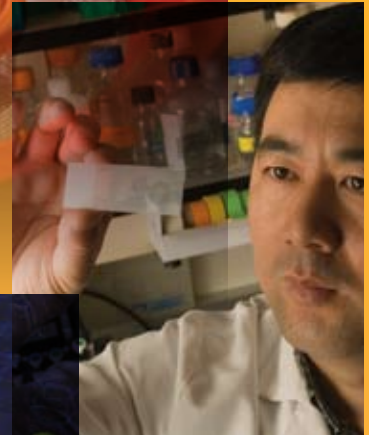
Preclinical studies conducted by Calando Pharmaceuticals suggested that nanoparticles containing siRNA to inhibit RR can serve as safe, effective drug-delivery vehicles. Plans for a clinical trial with cancer patients are already under way.

2004

Brainstorming session with Mark E. Davis, Ph.D., CalTech, and Yun Yen, M.D., Ph.D., and Stephen J. Forman, M.D., both from City of Hope

2005

Animal study
June 2005



City of Hope researchers pursue intra- and inter-institutional projects to find more effective anticancer agents.

Preclinical study
December 2005

2006

FDA approval
given for clinical trial
March 2006

First patient enrolled
into clinical trial
July 2006

Three-dose-level testing
December 2006

2007

Abstract submitted at American Society
of Clinical Oncology annual meeting
January 2007