

BSTANFORD TECHNOLOGY BRAINSTORM



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Granulysin: A Powerful Agent to Eradicate Microbes

What could be better than a molecule that kills *Mycobacterium tuberculosis*? How about an agent that also kills *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans* and numerous other infectious agents.

Steffen Stenger, Dennis Hanson, Alan Krensky and Robert Modlin discovered that granulysin, a protein found in granules of cytolytic T lymphocytes (CTL) and natural killer (NK) cells, has such broad antimicrobial effects. The group's discoveries on the effect of granulysin on *M. tuberculosis* and

other bacteria were reported in the October 2, 1998, issue of *Science*, in an article entitled "An Antimicrobial Activity of Cytolytic T Cells Mediated by Granulysin."

Krensky, Shelagh Galligan Professor of Pediatrics at Stanford University, originally discovered the molecule in 1987, then dubbed 519, but only discovered its killing properties a few years ago. The molecule was named granulysin due to its location in the cytotoxic granules of CTL and its lytic

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Start-Ups: A Few Points From the Initiated

Silicon Valley could also be known as "Entrepreneur Valley" due to the number of companies started each year. At times, it seems that every person in the Bay Area is developing a new company or is involved with a start-up in some way.

OTL is well aware of the entrepreneurial drive at Stanford and on April 12, 1999, sponsored an event intended to educate would-be company founders. Three speakers shared their insights on both starting companies themselves as well as working with new-born companies. The panelists (Guy Kawasaki, Lawrence Steinman and John Cioffi) and the insights they purveyed are highlighted below.

• **Guy Kawasaki** is co-founder of Garage.com, a company that "helps entrepreneurs and investors build great businesses" and author of multiple books including *Rules for Revolutionaries*.

The message from Kawasaki was a list of things NOT to do. Do NOT:

1. Use your uncle the divorce lawyer for your securities work.
2. Look for valuation, not value, when it comes to

investors.

3. Be paranoid and try to get everyone to sign a Non-Disclosure Agreement.
4. Submit a 100 page business plan and 60 slide PowerPoint™ presentation.
5. Send this plan straight over the transom to VCs with no introduction.
6. Ask for more than you need.
7. Keep burn rates high and cash balances low.
8. Believe that patents and intellectual property make your company defensible.
9. Wing it in your presentations.
10. Spend all of your time "proving" you can do the product and none of the time proving the existence of a market for it.

• **Lawrence Steinman** is a Professor of Neurology at Stanford and co-founder of Neurocrine Biosciences. Steinman advised:

1. You cannot start a company without attractive intellectual property. File timely invention disclosures with OTL. Follow these with patent applications and CIPs.

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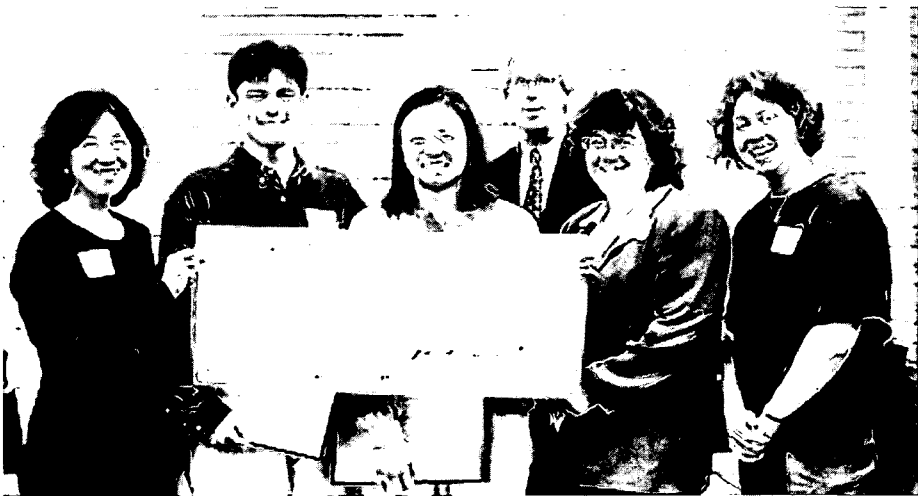
Anastomosis Invention Challenge

In order to promote creativity, collaboration and superior medical devices, OTL and the Medical DeviceNetwork (MDN) issued an "Invention Challenge" in Fall of 1998 (see *Brainstorm*, Fall, 1998). The challenge put forth to the Stanford community was to create a better approach to anastomosis, a method for joining blood vessels.

Current approaches to anastomosis with surgical sutures are time consuming and difficult. It is now preferable in coronary bypass surgery to keep the heart of the patient beating throughout the surgery. Therefore the anastomosis must be quick and precise.

The new approach had to be absolutely "leak-free," join the two vessels without any flow obstruction, and be relatively quick to perform. Submissions were due January 29, 1999, and from the twelve entries received, three finalists were announced in early March. The finalists had to make a presentation to the selection committee, a group consisting of people skilled in medicine, patent law and engineering. The selection committee evaluated the inventions on how well they would work, the likelihood that the invention could be manufactured, the cost of the final product, the invention's ease of use, and whether the invention was patentable (novel and unobvious).

The winners were announced on March 24,



A \$2500 check presented to the winners of the Anastomosis invention challenge. From left to right: Katharine Ku (Director of OTL), Walter Stevens (SU Graduate Student), Eunice Chen (SU Research Assistant), Paul Yock (Director of MDN), Sandra Miller (MDN), and Jessica Smith (OTL).

A Sampling of Licenses Granted by OTL in the Last Quarter

Docket(s)	Title(s)	Uses	Licensee(s)	License Type
S89-139	"Novel Insect Steroid Receptors"	Gene Therapy	Rhom & Haas	Field Exclusive
S93-169	"CMOS Area Image Sensor"	Image Sensoring	Canon	Non-exclusive
S93-192	"Total Access System Software"	ADA Workstations	Synapse	Field Exclusive
S96-017	"Gene Causing Epilepsy: EPM1"	Diagnostics	Athena Diagnostics	Exclusive
S97-122	"Optimal Analog Circuit Design"	Analog Design and CAD	Barcelona Design	Field Exclusive
S98-071	"Clasp-1"	T-Cell Regulation	Arbor Vita	Exclusive
S98-092	"Feline Immunodeficiency Virus"	Retroviral Screening	Rigel	Non-exclusive
S98-202	"Adenoviral Production Vector"	Production of Adenovirus	Clontech	Non-exclusive

1999. In first place, receiving a prize of \$2500, were Eunice Chen, Jessica Smith and Walter Stevens (pictured below). Two teams were designated as "runners-up" and were each awarded a prize of \$500. The runners-up were the husband-and-wife team of doctors Elisabeth and Allen Jeremias, both post-doctoral researchers, and Brian Courtney and John MacMahon, two post-grad engineering students. Since these inventions are not public yet, full descriptions are not currently available. However, OTL has filed a patent application based on the winning entry.

The next invention challenge begins in the Fall of 1999. The challenge is to invent a system for minimally invasive treatment of the arthritic knee. There are numerous approaches to solve this problem, so again a team well diversified in backgrounds (medicine/engineering) will most likely benefit from their teammates' experiences and education. Flyers will be posted around campus, and a full description will appear on MDN's homepage, <http://mdn.stanford.edu>.

New Equity Policy for Stanford University

On occasion, OTL takes equity as partial consideration for a license. The equity policy was recently revised, as recommended by the Committee on Research, endorsed by the Cabinet and approved by the Finance Committee of the Board of Trustees on June 11, 1999. Under the revised policy, equity is distributed as follows:

- 15% is allocated to OTL for its administrative fee;
- Inventors receive 1/3 of the remaining equity; and
- The OTL Research and Fellowship Fund, administered by the Dean of Research, receives the remaining 2/3.

If you have any questions regarding the policy, please contact OTL at (650) 723-0651. ▲

Granulysin...

Continued from page 1

function. It was found to be lytic against a variety of tumors and other cell types in tissue culture.

Krensky and Modlin, a professor in the Departments of Dermatology, Microbiology and Immunology at UCLA, teamed up in 1997 to test the hypothesis that granulysin would be able to lyse bacteria and other microbial pathogens. Stenger, at the time a post-doctoral student in Modlin's laboratory, first showed that granulysin was able to lyse *E. coli*. Further research revealed that granulysin can kill a variety of bacterial targets. Modlin had published an earlier paper in *Science* that showed that different types of cytolytic T lymphocytes had different lytic activities against *M. tuberculosis*. Krensky and Modlin collaborated to test whether granulysin was the missing link, a heretofore unknown antimicrobial peptide produced by CTL and NK cells.

The *Science* article details the researchers' experiments in which granulysin directly killed extracellular *M. tuberculosis*.

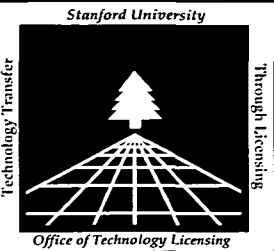
However, when granulysin was added to *M. tuberculosis*-infected human macrophages, no significant antibacterial activity was detected. The researchers guessed that the inactivity was due to the inability of granulysin to access the intracellular area where the mycobacteria resided. Therefore, they added the membrane-cutting molecule perforin, another agent from CTL granules, to the granulysin dose applied to the macrophages. Although neither granulysin nor perforin alone is an effective treatment against intracellular *M. tuberculosis*, the duo of proteins killed significant amounts of the infectious bacteria.

Granulysin may be an ideal antimicrobial agent since it is found naturally in our bodies, and the immune system would therefore not attack it. Side effects such as unwanted immune responses that are common problems for non-natural antibiotics would not be exhibited in the cases of granulysin or perforin.

By utilizing scanning electron microscopy, the researchers found that granulysin alters and distorts the bacterial surface of *M. tuberculosis*. Krensky and Modlin are conducting further studies on the mechanism of action of granulysin. Understanding how granulysin works may provide methods to screen for new antibiotics and new targets for cytotoxicity.

Granulysin may also be useful in treatments for cancer and viral infections including HIV. Research in these areas is also being explored.

With the current rise in *M. tuberculosis* and other infectious disease cases around the world and the decrease in effectiveness of many antibiotics, new therapeutics are critical for the health of the world's population. Granulysin may be the key to multiple new antibiotics as well as new screens and antibacterial products. Stanford is seeking licensees to further develop the granulysin technology. Since granulysin is a protein with a wide variety of possible uses, multiple licenses may be granted. Broad patent coverage is currently pending, and copies of the patent applications are available under a signed confidentiality agreement. Please contact Kirsten Leute at (650) 725-9407 or e-mail kirsten.leute@stanford.edu for more information. ▲



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above address.

Recently Issued U.S. Patents Available for Licensing from Stanford

Docket No.	Title	U.S. Patent Number	Issue Date	Inventors
S92-093	Inhibition of Proliferation of Vascular Smooth Muscle Cell	5,869,462	February 9, 1999	Victor Dzau
S94-040	Cache-Based Logging	5,893,155	April 6, 1999	David Cheriton
S95-036	High Frequency Contact Sampling Probe w/ Sib-Micron Spatial Resolution	5,847,569	December 8, 1998	David Bloom Francis Ho
S95-086	Micromachined Fluidic Coupler	5,890,745	April 6, 1999	Gregory T. Kovacs
S96-048	Reference Carrier Phase Prediction for Kinematic GPS	5,903,236	May 11, 1999	David Lawrence
S96-115	An Mdr1 Gene Mutation Resistant to Modulation by Cyclosporins	5,830,697	November 3, 1998	Gang Chen Branimir Sikic
S97-002	System and Method for Multi-resolution Scalable Audio Signal Encoding	5,886,276	March 23, 1999	Scott Levine Tony Verma
S98-031	Safety and Prefilled Syringe	5,865,227	February 2, 1999	Brian Carilli



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Brainstorm is now accepting advertisements from companies based in California. And the first ad is on us!

OTL is providing this as a service to Stanford students. Each advertisement will be approximately 1/4 of a page. The company can either supply its own description or we can build one for you.

Brainstorm's current circulation is around 3,000 issues per quarter, and it is distributed widely around the Stanford campus as well as to companies and other universities across the world.

The first issue is free. If your company decides to continue the advertisement, the cost is either \$150 per issue or \$500 for one year (four issues).

For more information, please contact Jill Brigham at jill.brigham@stanford.edu or (650) 725-9112.



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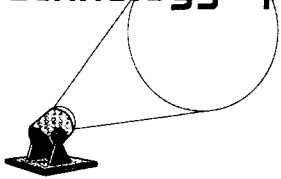
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Technology Spotlight: Recall



Recall, created by Sam Yen, Renate Fruchter, and Larry Leifer of the School of Engineering at Stanford, is a new application to radically improve video indexing. Recall holds

promise for enhancing and speeding up content generation and archival conjunction with software of many types including applications for video conferencing, distance learning, CAD, and corporate training by indexing audio and video with simultaneous sketching activity.

Recall is a drawing application written in Java that captures and time stamps each individual action on the drawing surface. The application also synchronizes with audio/video capturing and encoding through a client-server architecture. Once the session is complete, the drawing and video information is automatically indexed and published on a web server. This allows for distribution and synchronization playback of the drawing session and audio/video from anywhere at anytime.

In addition, Recall enables the user to navigate through the session and interactively jump to each part of interest by selecting individual elements in the drawing.

Recall is the only known tool that both replays and controls sketching concurrently, thereby eliminating the time normally needed to index the recorded section.

Stanford has filed for a patent on Recall and is seeking licensees. For more information, please contact Mary Watanabe at mary.watanabe@stanford.edu or (650) 725-9411. ▲

Start-Ups: A Few Points From the Initiated

Continued from page 1

2. Exclusivity is an asset with inventions that may be therapeutics for diseases. Techniques may benefit from "open architecture" non-exclusive licenses, although experience shows that even with techniques, exclusivity may be a benefit.
3. It is a major asset to work with the world's leaders in VC on Sand Hill Road.

• **John Cioffi** is an Associate Professor of Electrical Engineering at Stanford and co-founder of Amati Communications.

Cioffi drew on his experience by noting these following keys on start-ups:

1. Strong advantage (technology companies often have technical innovation, but not the only way to do it) and supporting theme.
2. Talented people
 - Stanford University students! (maybe some Cal people also)
 - Management:
 - attract other talent and let them know you value them
 - motivate those talented people with clear goals
 - then, let them do their job and continue motivation
3. Don't give up! (unless you're convinced you were wrong)

OTL plans to host a full-day event on start-ups in the fall. We encourage those with an interest in starting their own businesses to take advantage of the resources available in Silicon Valley and elsewhere. For a listing of some of our entrepreneur information, please visit our homepage at <http://www.stanford.edu/group/OTL/> and click the "Entrepreneurial Info" button. ▲



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