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TO: SVP
XYZCO

Strictly Confidential

FM: Jim Henry, Sag Harbor Group

RE: COMPETITIVE STRATEGY PROPOSAL -- PROTEOMICS

Date: December 23, 2000

I. INTRODUCTION

This proposal follows up on our conversations with you and other senior managers at XYZCO. It describes how Sag Harbor Group might be able to help you evaluate and act on some of your most important competitive strategy issues. It summarizes our understanding of your accomplishments to date, potential markets, competitors, and strategic priorities, describes the key issues that we propose to address, and provides an initial estimate of our timing, required staffing and fees. We have also attached brief biographical sketches for the SHG team members that we have assembled to work on this project.

As we've indicated, we are very impressed by your accomplishments, and excited about your prospects. We look forward to working closely with you on this important, incredibly interesting project.

II. BACKGROUND – XYZCO'S SITUATION.

Founded in 1995, XYZCO has already made significant progress toward its goal of becoming a leading supplier of "molecular pathology" and gene/ protein localization services to the global pharmaceutical and biotechnology industries. At the risk of restating facts that are already well known to you, just to put the team on the same page, XYZCO's key accomplishments including the following:[1]

- *Outstanding Technical/ Managerial Team*. XYZCO has assembled a top-notch managerial and technical team with a strong combination of skills in the "cross-fertilizing" disciplines of molecular biology, pathology, gene/protein expression, and bio-informatics. This team includes at least 15 PhDs and a cadre of senior managers with extensive drug company and venture management experience, and strong reputations in the biotech industry.[2] The team as a whole also appears to enjoy working together -- the company's "mood" is one of enthusiasm, optimism, and inquisitiveness. Of course there is also a concern that (a) everyone is stretched by day-to-day operating imperatives, and (b) overall strategic issues may need more attention.

- *Unique Human Tissues Bank*. XYZCO appears to have built a unique supply chain for normal and diseased human tissue, based on close relationships with local hospitals. This, in turn, has permitted it to establish one of the world's largest private tissue banks for diseased and normal

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tissue, with 2 million archived, indexed, and imaged specimens representing all major disease and organ groups, demographic variables, and a time series of tissue specimens that is especially useful for controlling for age effects in disease progression.

- *Fee-for-Service Contract Research Business/ Customer Base*. Since October 1997 XYZCO has undertaken more than 130 gene expression, drug target validation, and protein localization research projects for about 50 companies, including 25 of the top 40 in the global pharmaceutical industry.[3] This contract research (CRO) business, based on standard in-situ hybridization (ISH), high-density array (HDA), and immunocytochemistry (ICC) localization techniques, has provided the foundation for XYZCO's revenue growth – last year it accounted for more than eighty percent of revenue, and this year it will still account for at least thirty-forty percent. While this fee-for-service business has only produced modest gross margins, and project profitability has been highly variable, XYZCOis developing automated approaches to these techniques that it believes will improve throughput and productivity dramatically.

- *Proprietary Gene Expression/ Protein Localization Data Bases.* The "mission statement' in XYZCO's 1999 Annual Report states that the company's key goal is to "be the first company to offer a comprehensive, integrated database that relates nRNA levels to protein expression and localization data in human disease." XYZCO has indeed begun to develop and license its own proprietary, multi-client data base. Unlike other "gene expression" databases offered by companies like Incyte, Millenium, and Celera, XYZCO is focusing on the relationship between protein expression and diseased tissue, and is combining a variety of "curated" data from publicly-available gene sequencing data bases with proprietary genes and tissue bank-based data on cell mRNA expression, protein expression and localization.

  To deliver this unique data base, XYZCO is investing heavily in "bioinformatics" infrastructure, including imaging software, slide digitization technology, and network infrastructure. The first installment of its data bases targets the "GPCRs"[4] protein family, a high priority in the industry for drug development. To data XYZCO has succeeded in signing up at least 3 "big pharma" subscribers to the GPCR data base, with several more in the wings. It has plans to follow up on this GPCR data base with several others that address at least a dozen other protein families.

- *Tissue Image Archive/ Pathology Services/ Virtual Pathology*. Closely related to this bioinformatics effort, XYZCO has defined itself as a "molecular pathology" company, focusing on the genetic basis of disease. To support this activity, as noted, it has assembled the world's largest tissue banks, and is now building a huge digitized, indexed image archives of diseased tissue slides. It has plans to offer "remote" pathology services that leverage the use of this archive. It is also developing specialized tools and pattern-recognition techniques that may permit it to automate such pathology analysis, and distribute them over the Web.

- *Gene Discovery and Patents.* While gene discovery and therapeutics have not been a focus of XYZCO's strategy, as a byproduct of its own research and contract projects, it has identified and filed patents for more than 300 new genes that it believes may be associated with conditions like aging, cancer and baldness.

- *Funding.* To finance these efforts, XYZCO has raised about $23 million in private equity, and will end the year with almost $10 million in cash on hand, nearly enough to finance its current

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"burn rate" -- $4 million a year – all the way to break even in 2002. However, one of XYZCO's key financial objectives now is not simply self-financing, but to prepare to "go public," capitalizing on the fact that public markets have recently valued companies in the proteomics arena at revenue multiples of 25-100x or more. (See below, Table 1.)

III. KEY MARKET AND COMPETITIVE DEVELOPMENTS.

While XYZCO has been developing along this path, customers, technology, partners, and competitors have also been developing rapidly, so that the company now faces a set of very complicated strategic choices.

(1) High-Growth (Potential) Market(s). The "good news" is that the *overall* market(s) for localization services, proteomics, and virtual pathology appear to be moving in XYZCO's direction. Powered by productivity improvements like automated DNA sequencers, differential displays and micro-arrays, the task of sequencing the human genome's 3.5 billion DNA base pairs that was started in the mid-1980s is now virtually complete, and the biotech and pharmaceutical industries are turning their attention to the next question – what is all this genomics information good for?

More precisely, the next stage of molecular biology's development is to understand the causal association between particular diseases/undesirable conditions and particular genes or proteins, and to design specific molecules to affect them. As many commentators have recently observed, this task probably dwarfs the task of genome sequencing in its difficulty.[5]

While there may be between 30,000 and 120,000 human genes,[6] scientists now know the approximate functions of only about 15,000 of them, and they have so far targeted only about 500-600 for drug discovery. Furthermore, the molecules that carry out gene instructions and are the most important "proximate causes" of non-infectious diseases like Alzheimer's or lymphoma are proteins, not genes. There is only an imperfect correlation (<.5) between protein function and particular genes. There are also up to 10 times as many disease-relevant proteins as human genes, and an even large number of so-called "post-transcription" influences on protein function and inter-protein interactions that can swamp the determinism of genetic encoding.

Overall, given the plethora of new genes and proteins, drug companies are now swimming in thousands of potential therapeutic targets, and are in a global footrace to evaluate, develop and patent them. This *may be* very good new for XYZCO.

(2) Scarce Skills/ Increased Drug Industry Outsourcing and Partnering. Protein-disease associations are often only clearly identifiable in the context of specific cell types or organs, using pathology-based techniques – e.g., to paraphrase the great Princeton statistician John Tukey, "Just look at the f...kin' (data) cells!!!" Traditionally, this has required live pathologists to *look at images of* diseased tissue in order to correlate visual patterns with developments at the molecular level. While several biotech companies have recently been trying to automate various types of protein/ disease image analysis, this is clearly a wide open, high-priority arena for proteomics research and drug targeting.[7]

For purposes of sorting out protein targets, validating disease associations, and avoiding unwanted side-effects, the key disciplines required are precisely those that XYZCO has

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assembled – a combination of protein/antibody expression analysis, pathology, bioinformatics, and gene identification.

The other key claim is that few drug companies have significant skills in these areas – especially molecular pathology.[8] While drug companies have a long history of targeting protein families for new drugs,[9] they remain dominated by chemists rather than biologists, much less pathologists. And while "rational drug design" has been an industry buzz word since the l980s, preclinical drug discovery – on which the global industry spends $27 billion a year[10] -- still leans heavily on "black box," theory-free methods. In crude terms, basically this amounts to screening thousands of plants and microorganisms with bioassays to find new compounds, and then essentially throwing these against the wall to see what sticks.

Of course we can make too much of theory – recall the French academic who asked, "Yes, yes, we know it works in practice. But does it work *in theory*?" And the high average cost of new drug development – $1 million per day for three-five years – is partly due to heavy post-clinical expenses associated with regulation and testing. But since only a small fraction of targets ever reach testing,[11] and many false paths might have been avoided with greater use of expression-based targeting and toxicology, from this angle much of the waste in drug development might also be attributed to the prevalence of the "chemist culture" and the industry's "pre-genomics" scientific methods.

In any case, it appears that leading drug companies are now (just) beginning to recognize their own skill deficiencies in these new areas, and are more willing to seek these skills outside, through a combination of contract research, pre-packaged gene/protein expression databases, and strategic partnerships. As Table I below indicates, there is now a growing number of such relationships in the emerging proteomics industry, with leading pharmaceutical companies like Pfizer, Novartis, Squibb, and Hoffman LaRoche diversifying their risks by contracting and partnering with multiple independent research, data base, and "collaboration" suppliers.

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Table 1. Leading Players, Partners, and Customers, Proteomics Industry (Dec 2000)

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Company	LifeSpan Bio	Pharmagene	Cambridge Antibody	Incyte Genomics	Oxford GlycoSciences	CuraGen	Rosetta Inpharmatics	Gene Logic Inc
Symbol	-	LSE:PGN	LSE:CAT	Nasdaq:INCY	Nasdaq:OGSI;LSE:OGS	NASDQ:CRGN	Nasdaq:RSTA	Nasdaq:GLGC
Founded	Sep-95	Mar-96	Jan-90	Apr-91	1995	1993	1996	Sep-94
Marketcap (12/6/2000)	na	$83.2mm	$1.212 billion	$2.0 billion	$808mm	$1.63 billion	$592mm	$556mm
Employees (12/99)	70	54	146	1108	147	309	150	176
Focus	Mol.Path/functional gen.services (CR, DB)	Mol.Path/functional gen.services (CR, DB, DV)	Func. Genomics/Antibody therapeutics	Genomic info db co/gene exp.Services	Proteomics/microarrays	Func. Gen services platform; therantibody and protein devel.	"Informational genomics" (tools co.)	Gene expression db and tools
Revenue (2000e$mm)	$4.1	$1.31	$2.69	$185	$13.10	$20.40	$5.30	$22.5
EBITDA (2000)	?			($22)		($24)	($30)	($32)
Cash on hand (12/2000)	$9.5(?)			$645		$245	$159	$231
Key partners								
Abbott Labs				ilsilicoSNPdb			Info system develop	
Abgenix						$50mm equity + $200 mm R&D		
Affymetrix				Law suit-patents			Info system develop	TP-microarrays
Agilent (HP)							Channel partner	
AHP (Wyeth-Ayerst)	**CR**		**Drug devel - cash, royalties, targets**	**Microarray Tech, LifeSeq™ DB**				**CDB - predtox.; GeneExpress™ Sub**
Akso Nobel (Organon)								CDB - fertility, CSN
Allergan		Pharmbase™						
Ares-Serono	CR							
AstraZeneca	**CR**	**CR**	**Research collab. - cash, targets**		**DB customer - Incyte/OGS LifeExpress**			
Avalon Pharma								GeneExpress™
Aventis	**CR**			SNP Discovery				
BASF		CR	Drug devel - cash, royalties					
Baybr College of Med				Collab				
Bayer		CR		LifeSeq™ Gold DB	2 yr program - protein targets for asthma, COPD			
BD								
Biogen				Genomics partnership		CR		
Boehringer	CR							
Bristol Myers-Squibb	**DB**			**LifeExpress™ DB**	**DB customer - Incyte/OGS LifeExpress**			
Cambridge Antibody					Strategic alliance in Protein Microarrays			
CellTherapeutics	CR							
Cept	CR							
Chiroscience		CR						
Chugai	CR							
COR Therapeutics						CR		
Corixa				Vaccine discov partnership				
Cubist		CR						
Dendreon	CR							
Dupont	CR					CR		
Elan	CR							
Eli Lilly			License (cash) Ther.Protein devel, SNP db royalties, targets)					
Fermtg		CR						
Galapagos				Func.Genomics Collab				
GeminiGenomics						CR	Info system develop	
Genaissance								TP-gene specific SNPs;
Genzyme	CR							
Genentech			License (cash, royalties)			CR		
Gene Logic				Law suit-patents				
GlaxoWellcome	**CR**	**CR**			**Multidisease biomarker collaboration (12/4/2000) for high-thruput**	**CR**		
George Wash U.	CR							
HGS			Drug devel - cash, royalties					
Hoffman LaRoche	**CR**					**CR**		
Icagen	CR							
IBM				Tech partner				

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Table 1. Leading Players, Partners, and Customers, Proteomics Industry (Dec 2000) (Continued)

Company	LifeSpan Bio	Pharmagene	Cambridge Antibody	Incyte Genomics	Oxford Glyco Sciences	CuraGen	Rosetta Inpharmatics	Gene Logic Inc
ILEX								
Immunex	**CR**		**Drug develop deal**					
Incyte Genomics					Nonexclusive gene expression db -- combined with Incyte's LifeSeq™			
Isis	CR							
Invitrogen								TP-seq, clones of major disease genes
Janssen	CR							
Kanebo	CR							
Japan Tobacco								CDB - renal,
Kirin	CR							
Kyowa HG		CR, Pharmbase™						
Loreal	CR							
LG Chemical								CDB -;
Mederex					Therapeutic antibodies alliance			
Merck					Proteomics for diabetes			
Monsanto	**CR**						**Infosystem devel**	
Motorola				License for Biobarrays				
NeuralStem								GeneExpress™
Novartis	**CR, DB**	**CR**						
OGS		CR		CoTab - LifeSeq™ DB				
ONO Pharma	**CR**					**CR**		
Ontogeny	CR							
OSI Pharma	CR							
Oxford BioMedica		Pharmbase™						
P&G Pharma								CDB - osteoporosis
Packard BioSciences					Alliance to develop protein biochips			
Parke-Davis	CR							
erkins Elmer (PE Biosystems)				cDNA Licensed	Proteomics development			DB Devel
Pfizer	**CR, DB**	**CR**	**License (cash, royalties)**		**Collaboration - new proteins for Alzheimers, atherosclerosis**			**GeneExpress™ Sub**
Pharmacia	**CR**		**License**					
Psychiatric Genomics								GeneExpress™
Quintiles					Proteomics-based toxicology service			
RCIC				Lung cancer genetics				
Regeneron	CR							
Rhone-Poulenc	CR							
Roche	**CR**					**CR**		
Sanofi-Synthelabo	CR							
Sangamo							Infosystem develop	
Sankyo		CR		LifSeq™ DB				
Schering AG	**CR**							
Schering-Plough	CR							
Scripps	CR							
Searle			Drug devel - cash, royalties					
Sequenom				SNP Assays CoTab				
SmithKline		CR						DB Devel
Stanford U	CR							
Sugen	CR							
Symbol								
Taisho	CR							
Tularik	CR							
UCB Research								CDB - asthma, allergies;
Vernalis Ltd		CR						
Vertex				Genomics partnership				
Warner Lambert								
Yamanouchi	CR							
Zymogenetics	**CR**		**Research coTab - cash**					
Zyomyx			Drug Devel					

(3) Many New Potential Competitors/Partners On the Horizon. While the arenas of proteomics, localization research, bioinformatics, and virtual pathology are still quite new, several potential competitors for XYZCO are already visible on the horizon. This is by no means a purely negative development, because in nascent markets it often helps to have competitors around to share the costs of creating standards and educating customers and partners about the value of new technologies. (Indeed, one of our hypotheses is that XYZCO may need to "get out more" in the sense of proactive marketing, working with some of its competitors to raise the industry's profile, set standards, and define categories.)

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However, given the fact that drug industry research is (increasingly) concentrated in the hands of less than fifty companies, that research spending on XYZCO's specific gene/protein families and techniques is even more concentrated, and that having to deal with competitors forces XYZCO to become clearer about its own positioning, it is helpful to keep a weather eye on this competitive activity.

The following competitive survey is preliminary. However, as usual, some things can be said:

- **Across-The-Board Competitors.** To date only one other company, UK-based *Pharmagene PLC* (www.pharmagene.com) has adopted a business model that is virtually identical to XYZCO's, combining (1) a proprietary human tissue data base, (2) contract research on gene/protein localization, and (3) proprietary gene/ protein expression databases. Pharmagene also indicates that it is pursuing (4) in-house therapeutics development, at least up to clinical testing. In this record, Pharmagene's financial performance may be an ill omen, or just due to its own unique missteps -- founded in March 1996, and funded by the leading UK venture capital firm 3i, Pharmagene went public this past August on the London Stock Exchange, reached a peak of 360 p per share in August, and then plummeted in December to 100 p, yielding a market capitalization of just $80 million. In September it reported losses of about L –3mm L for the last six months, roughly the same size as XYZCO's.

- **Contract Research Competitors.** Several other contract research shops that offer gene /protein localization services have become more visible in the last few months. Clinomics Laboratories Inc. (www.clinomics.com), a privately-held company based in Massachusetts and Maryland, purports to offer a wise range of proteomics-related services, including gene profiling, tissue micro-array, gene/mRNA/protein extraction, and tissue repository services. It also claims to be developing its own "genomic medicine databases." Immunex (www.immunex.com) and CuraGen (www.curagen.com) are other functional genomics/ proteomics company that provides a variety of contract research services for drug development partners.

  While XYZCO arguably offers the broadest, highest-quality contract services in these areas , and while it has advanced plans to increase its own CRO productivity, these new competitors may lead to more price competition in the short run, at least for some customer segments, and force XYZCO to sharpen its offers and its focus on particular customer segments and services.

- **Human Tissue Banks/ DNA Sample Repositories.** An increasing number of biotech, medical, and pharmaceutical players are also beginning to accumulate expanded human tissue banks. As noted, Pharmagene PLC is already expanding its tissue banks, based on relationships with several UK hospitals. Nonprofit hospitals like Sloane Kettering, Beth Israel, and Columbia Presbyterian are also building tissue banks. Several drug companies, like Squibb, may be doing the same thing – although it appears to be going slowly. Leading genomics companies like Gene Logic (www.genelogic.com), Incyte Genomics (www.incyte.com), and Celera Genomics (www.celera.com) have also started to gather proprietary collections of human DNA and tissue specimens.[12] In September 2000 privately-held Ardais Corp. (www.ardais.com) announced that it had enlisted Duke University and Beth Israel Hospital as charter partners (with 5% equity ownership each), and was trying to acquire a large repository of "waste tissue" specimens and dna for clinical use. Privately-held San-Francisco-based Clontech (www.clontech.com) and DNA Sciences (www.dna.com) are also entering the tissue and dna specimen collection arenas,

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although each is focusing on different segments.[13] The Genomics Collaborative (www.getdna.com), a 1998 Cambridge Ma.-based startup that claims 200 physicians and hospital research sites in its Global Physician Network™, says that it is developing a Global Repository™ of human tissue, serums, and dna, intended to contain 100,000 samples with detailed phenotypes this year and 500,000 by the end of 2003.

Overall, XYZCO is well in the lead so far as the scale and quality of its human tissue bank is concerned, and several of these players will either focus on different market niches or keep the tissue banks only for their own use. However, it may also be important to recognize that XYZCO's advantage here is not permanent. Especially for research that doesn't require huge collections of tissues, XYZCO will have to devote more attention to service and other "non-scalar' distinctions of its tissue collection and image archive.

- **Gene and Protein Expression Databases** (**and Nifty New BioInformatics Tools**.) While so far only Pharmagene claims to be offering a protein expression data bases that is anything like XYZCO's, there are a plethora of *potential* competitors. These include companies like Incyte and Celera that have may have already sold out customer segments for their gene expression data bases, and are now looking for other data bases to offer. It may also include so-called "informational genomics" players like Rosetta Inpharmatics (www.rii.com) that had been focusing on providing analytical tools for genomic analysis, but now, in the context of new collaborations with drug companies, may be developing proprietary databases on protein expression and toxicology.

- **Protein Expression/ Diseased Tissue Imaging.** There are several biotech companies operating in the broad area of "high speed proteomics image analysis," correlating various kinds of protein expression with diseased tissues, in order to accelerate drug discovery. The leaders include Scimagix (www.scimagix.com), Oxford GlycoSciences (www.ogs.com), and Millenium Pharmaceuticals (www.mlmn.com). Depending on the company, and the success of their techniques, these may turn out to be important competitors *and/ o*r interesting partners for XYZCO.[14]

- **Virtual Molecular Pathology.** While remote pathology -- viewing images on computer monitors rather than directly through light microscopes --- has been around for at least a decade,[15] there has also recently been increased activity in this arena. This activity – part of a more general surge in telemedicine[16] -- is driven by several factors:
  - The proliferation of technologies that facilitate wide-area image networking, especially Internet access, bandwidth, and security; digital imaging, especially high-speed, high-magnification slide digitization; store-and-forward image management; and real-time "robotic" microscopy.
  - The rising demand for pathology services in many countries, relative to supply;
  - The consolidation of pathologists into specialized laboratories, permitting them to concentrate on niches like dermatopathology, surgical pathology, hematopathology, and cytopathology;

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- The growing "capitalization"[17] of pathology, supported by sophisticated new diagnostic techniques like flow cytometry, immunohistochemistry, and molecular diagnostics; and

- The increasing geographic dispersion of clinics, yield a greater physical separation between clinicians and pathologists.

In the last decade many public and private institutions have recognized this conjunction of factors, and have entered the telepathology field, producing systems and services that seek to conserve pathology resources, distribute them more widely, and provide international access to libraries of pathology information – in the limit, a global system for distributing expertise and analysis, as well as images. So far little effort has been focused on molecular pathology, but that may not be far off.

Most of this telepathology activity has originated in the public or (at least) non-profit sector, sponsored by universities, hospitals, and governments. To cite a few examples:

- With the help of US government grants and technology partners like Roche and LanVision, the University of Pittsburgh Medical Center (www.pathology.pitt.edu) has developed a Web-based ":Laboratory Information System" for managing the capture, distribution, and analysis of pathology images. It has assembled a digital image archive with 30,000 images. The University intends to offer web-based consultation services, first relying on its own archive and Web-based store-and-forward image networking.

- Another active player here is the US Armed Forces Institute of Pathology (www.afip.org). It has a staff of 120 pathologists that are providing about 60,000 virtual "second-opinion" consultations a year, using the Bacus Internet-based store-and-forward imaging system and its BLISS™ system for slide digitization. (See below)

- The US DOD's "Telemedicine and Advanced Technology Research Center" (www.matmo.org) is actively supporting the development of telepathology, including digitization and cataloging of tissue samples, pattern recognition, and "telegenetics," a web-based genetics consulting applications. The UK's DERA defense research facility has similar projects.

- John Hopkins University's Department of Pathology and the University of Maryland's Department of Computer Science (www.cs.umd.edu/projects/hpsl/ResearchAreas/vm.htm) have a joint project to develop a "virtual microscope," using Java applets that allows remote users to access pathology services without the need to install special client software.

- Oxford University's Department of Pathology at Nuffield has established a telepathology portal on the Web that provides a goldmine of information about activities in this field. (See www.ndp.ox.ac.uk/telepathology). Oxford has also declared its intention to offer remote consultative services, using telepathology tools. It has also developed automated techniques for high-throughput slide digitization.

- Histkom (www.ipe.uni-stuttgart.de) is a joint project of the University of Stuttgart's Institute für Physikalische Elektronik developed and Deutsche Telekom. It is

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developing telepathology services that DT hopes to market to clinics and laboratories as part of a "Global Healthcare" network solutions package. (…an interesting example of collaboration with a network services provider…)

- The Histkom effort builds on the EU- supported "EUROPath (European Pathology Assisted by Telematics for Health) project, a three-year effort that concluded in 1999. It tried to jump-start the development of remote image networking in order to serve Europe's 3000 clinics and 15,000 pathologists. The EU supported this effort because it wanted to reduce the 2 billion ECUs that it estimates are spent each year in Europe on 200 million microscope preparations. It also wanted to provide the foundations for an EU-wide "multimedia medical imaging platform." (How well it has succeeded is unclear.)

- In the last year the UICC (the Union Internationale Contre le Cancer) has established a Telepathology Consultation Center, headquartered in Berlin at the Institute of Pathology of the Charité, Humboldt-University**.** (See www.medstage.de/public.) The center is developing its own platforms for telepathology, teleradiology, and teleultrasound, and has assembled a panel of some forty expert pathologists from around the world to provide remote "second-opinion" services, using simple store-and-forward image distribution.

Private sector activity in the telepathology arena is also increasing. For example:

- Most leading optics manufacturers now produce robotic microscopes, and there is an growing supply of telepathology software to control them. Among the optics hardware leaders are Zeiss (cf. its 1999 US Patent #5949574 for a "computer supported video microscope") Nikon, and Olympus. Among the software providers, the Dutch company Zem (www.zem.com) has a distinctive Java-based telepathology imaging platform.

- Privately-held Apollo Telemedicine (www.apollotelemedicine.com), based in Maryland, claims to be the "premier provider of telepathology systems in the US," although its Web site only records one recent venture with a Kuwaiti company. (!). Its claim is partly based on its exclusive license to a 1993 US patent that was issued for "any system using a remote controlled robotic microscope to make pathology diagnoses." According toe CEO Mark Newburger, anyone even thinking of building a telepathology system for its own use in the US may need a license from Apollo. But that might be avoided simply by focusing on slide digitization [18]

- That is precisely the focus of another young telepathology systems company, Ilumea (www.illumea.com), based in Newport Beach, California, recently acquired by eMedsoft (www.emedsoft.com AMEX: MED). It offers Internet microscopy and remote imaging systems.

- Illumea's FiberPix™ system is just now being deployed by DIANON Systems (www.dianon.com; Nasdq: DIAN), which already offers contract services in anatomic pathology in Ohio, New York, Florida, and Connecticut, and is reported to be developing a nation-wide telepathology service.

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- Yet another telepathology systems supplier is Bacus Laboratories (www.bacuslabs.com). It developed the BLISS™ system, a robotic microscopy system with software that digitizes entire slides at high magnification. (Oxford University also claims similar technology, independently.) Bacus recently acquired US Patent #6,101,265, issued in August 2000, on a "method and apparatus for acquiring and reconstructing magnified specimen images from a computer-controlled microscope."

- Of course the "elephants in the hallway" in the medical imaging fields are companies like GE Medical Systems (www.gemedicalsystems.com), Siemens Medical Systems (http://www.sms.siemens.com), and Hitachi Medical (www.hitachimedical.com).so far none of them have declared a strategic intent to enter this field.

Overall, while there has been a growing level of activity in telepathology, and an increasing number of potential partners/competitors, the for-profit market is still very small, and it is not yet clear how large this services market will be and which business models will prevail. One key market inhibitor is the existence of regulatory barriers to cross-border (state or international) "virtual pathology" services.[19]

- **Alternative Approaches/ Technology "Wild Cards".** In addition to direct competitors, XYZCO may also face indirect competition from companies that are taking fundamentally different approaches to protein-targeted drug discovery. All the competitors noted above approach gene/protein targeting from the standpoint of conventional "small molecule therapeutics, in which drug discovery consists of (1) isolating key genes or proteins of interest, (2) ransacking expression data to find associations among between particular proteins and diseases; and (3) turning these results over to chemists who then work on "hits," targeting high-association proteins with compounds to see what sticks to the wall.

  One relatively new alternative focuses on producing and screening quasi–synthetic antibodies as therapeutic agents, in order to produce quicker and more precisely targeted results, at least for autoimmune illnesses like multiple sclerosis and arthritis. This approach, pursued by companies like Cambridge Antibody Therapeutics PLC (www.cambridgeantibody.com), Medarex (www.medarex.com), and Abgenix (www.abgenix.com), uses a variety of techniques to produce transgenic mice that can develop libraries of human monoclonal antibodies.[20] These antibodies appear to be significantly cheaper, faster, and more abundant to produce than those yielded by more conventional methods, including those used by XYZCO.[21] They not only can be used to understand protein impacts, but can also become therapeutic drugs themselves. While, as noted above, conventional *pre-clinical* drug development often takes at least five years, this approach can shorten that to as little as a year.[22] According to a recent survey by the Pharmaceutical Research and Manufacturers of America, antibodies already account for twenty percent of biopharmaceutical drug targets now under development.

  At this stage in our analysis, it is not clear how XYZCO should view this antibody route to therapeutics – as a substitute, a complement, or a largely orthogonal development. One hunch is that it might be attractive for XYZCO to seek a strong antibody partner, but this is only a "weak hypothesis" at this point.

IV. BEYOND CRO – XYZCO'S KEY STRATEGIC CHOICES

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This brief overview of market and competitive developments in this complex field is necessarily a bit superficial. However, it does at least show that while XYZCO has a strong base to build on, it also faces a growing list of strategic choices about precisely where it should position itself, how it should go to market, and with whom it should partner.

Another key fact is that while XYZCO's bread-and-butter has so far been contract research, this activity appears to be a relatively low-margin, increasingly competitive business.[23] As noted, XYZCO is taking steps now to improve contract management, contract pricing, and profitability, and is also investing in automation.[24] Our hunch, however, is that "this nice little CRO business" is unlikely to *ever* provide the kind of revenue growth and market multiples that XYZCO will need in order to go public.

So given its diverse portfolio of skills, the key question is, where else should XYZCO focus? On the one hand, there is an abundance of potential markets, business models, and partners. On the other, as you have indicated, one byproduct of your success is that there has been just too little time to think systematically about market strategy, competitive positioning, and strategic partnering. The tendency has been to "fly blind."

This is not unusual for young high-growth companies. SHG has recently worked with several that are in exactly this same situation. At this stage, business strategy becomes a matter of making very tough tradeoffs -- deciding to go in one direction rather than another. Indeed, one good test for whether or not a new company really even "*has a strategy*" is to ask, "What tradeoffs is it making? What has it *agonizingly decided not* to do?"

We propose to help you mount a concerted effort over the next few months to better understand your markets, customers, and partners, clarify your comparative advantages, define and compare your basic strategic options, evaluate them against clear criteria and the best available data – and decide what *not* and what *to* do.

This effort would not attend to short-term operational improvements or short-term marketing tactics, though we often do surface fruitful ideas in those domains as well. Rather, we'd like to focus on helping you make fundamental medium-term (1-3 year) strategic choices that could provide sustainable differentiation -- and that you might otherwise not find the time to make.

Our thinking about your strategy is obviously evolving, but at this point we propose to focus on (some combination of) the following critical issues.

(1) "What Is XYZCO's Database Strategy?" XYZCO is betting heavily that packaging its know-how and analytical tools in standard bioinformatics databases and/or image/archival products and services that are licensed to multiple subscribers can provide a much larger, more profitable business than CRO. This strategy appears to be working, at least in the sense that XYZCO has managed to "bootstrap" its CRO business into data base contracts with a half dozen drug companies However, our hunch is there are opportunities to refine this strategy with the help of customer inputs and market analysis. Among the key questions:

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- **Overall DB Market**. How large is the overall market for proteomics-related databases likely to be? What are the largest, fastest-growing customer segments in pharmaceuticals? in biotech? Is XYZCO's largest potential market among the largest drug companies, or the "next 500-1000?"
- **DB Competition/Industry Structure**. How should XYZCO position its offers against potential competitors? What are XYZCO's most important strategic assets/ comparative advantages in the database/image archive markets? What fundamental barriers to entry can it establish? What share of the overall potential market can XYZCO expect to command?
- **DB Customer Value.** What do customers want/expect from these new DBs? How do they evaluate whether purchasing them was valuable? Do they think about "substitution costs" when they estimate how much they are willing to pay? What is their experience so far with proteomics or gene expression data bases? How do they think about toxicology risk assessment, and the "insurance policy" that a toxicology service might provide?
- **DB Product/Services Design.** Precisely what "packages/slices" of data/images collections do (which) customers want, in what order? How much are customers planning to spend on which categories of protein targets? Which database services should XYZCO focus on delivering next -- for (a) curated data from public sources ? (b) proprietary data on particular protein families? (c) human toxicology screening databases? (d) pathology image archives? Does it make sense for XYZCO to become a kind of "ASP" in this arena, selling subscription services rather than whole databases? (..a sort of "Nexis" for proteomics) ?
- **DB Pricing.** What is XYZCO's longer-term pricing strategy for these databases? In the scheme of things, how important is price as a buying factor to which customer segments? How do potential buyers actually make data base purchasing decisions, and how does price figure in? Is there an opportunity to price closer to customer value? Subject to XYZCO's existing pricing commitments, precisely what is the pricing/ product segmentation model for new databases? Should they be offered for standard lump sum license fees, independent of use and the same for all subscribers; per seat licensing? pay per view arrangements? Standard pricing lists? Private custom-backed deals? Maintenance fees? Milestones for development, or royalties based on actual research output? Should there be "suite" pricing, to reward subscriptions to multiple databases?
- **DB Channel/Marketing Strategy.** Are there channel partners that XYZCO can enlist to help it bring its db products and services to a broader audience? Which geographies might be best served by this indirect channel approach?

- **DB Partnering.** Are there any technology partners or providers of complementary tissue banks, image archives, or data bases that XYZCO should consider partnering with, in order to strengthen its position in this market, create "defensive" barriers, and increase market access?

- **Overall DB Strategy Value.** Pulling together the overall outlook for XYZCO in the standard proteomics database market, what is the endgame? To what extent is this db market ever likely to generate the revenue, profitability, and valuation that XYZCO needs to meet its financial targets?

- **Alternative – Strategic Partnerships**? More broadly, are multi-client databases and archives the best way to monetize XYZCO's unique assets, or should it also consider more monogamous, bigger-ticket strategic partnerships? If it chose the monogamous route, what partners in drug discover/chemistry/databases look most interesting?

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(2) "What Is XYZCO's Virtual Pathology Strategy?" XYZCO's strategy for commercializing telepathology does not appear to be as far along as its data base strategy, but substantial investments are being made, the company may have a distinctive story to tell, and this emerging market appears to be developing rapidly. Many of the same questions that applied to the data base strategy are also relevant here:

- **Overall Virtual Pathology Market.** How large is this market likely to be? How quickly will it develop? What regulatory, technical, or other barriers could slow its growth? What will be the largest segments? What are the key growth drivers?
- **Industry Structure/Competitive Outlook.** Who are the leading players in the market? What's the outlook for the overall structure of the industry? Who will be XYZCO's main competitors? What are the key factors for success likely to be in telepathology – image archive size? digitization and image management? service partnerships? specialization in particular areas? Alliances with systems providers? Alliances with hospitals/ clinics/ laboratories?
- **Customer Value.** Can we quantify the economic advantages that telepathology may offer to potential customers? How does this vary by segment?
- **Business Models.** What are XYZCO's real comparative advantages here? What business models should it consider? How soon will its pattern recognition capabilities in this arena be marketable? Can it license its proprietary know-how and image archives to service providers or systems providers? Should it try to offer its own retail telepathology services? Can XYZCO acquire proprietary IP in this area?
  - **Potential Strategic Market/ Business Development Partners.** What strategic partners should XYZCO consider to jump-start its position in this market? Are leading medical systems providers like Siemens and GE interested? What about value-added network services providers or telcos? (DT, Qwest, UUNet, AT&T, etc.)? Leading regional hospitals? Other potential tissue collections? What other activities can XYZCO take to grow the market and enhance its own position? What strategic coalitions are likely to emerge in the industry? Which partners will be best to work with?
  - **Virtual Pathology Strategy Value.** How expensive and time-consuming will it be for XYZCO to develop, launch, and market these services? What is the potential payoff to XYZCO, in terms of revenue, profitability, and NPV? Should investments in this arena have priority over others?

(3) "**What Other Strategic Options Should XYZCO Pursue (If Any)?"** As noted above, XYZCO has a very wide range of technical capabilities and interests. At least in theory, therefore, it may have many other strategic options, in addition to the two just outlined. In the interests of "deciding what we are **not** doing (now)," it may be useful to gather these up, specify them more precisely, and screen them systematically, winnowing them down to those that we can afford. Among the candidates suggested by our interviews, company documents, and industry readings:

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- "Develop a business in proprietary bioassays/ ligand binding assays," presumably along the lines of Panvera (www.panvera.com) , Amersham, and Tropix.

- "Pursue proprietary gene and protein discovery, or and pre-clinical therapeutic discovery more aggressively," perhaps in partnership with a major pharmaceutical or biotechnology company.

- "Branch out into toxicology databases – perhaps even animal toxicology."

- "Partner with a leading antibody company, combining our two skill sets, and perhaps identifying therapeutic antibodies directly in the process."

- "Pursue an alliance with a major chemical company, focused on generating compounds that generate "hits" rather than just "'leads."

We propose to evaluate these and any other strategic options that might turn up against explicit criteria, including the following:

Strategic Options Assessment – Selected Criteria

1. **Stand-along value**
   - Potential market size and growth by segment
   - Comparative advantages, e.g.,:
     - Brand/ reputation
     - First mover/ fast mover/lead time
     - Learning/ know-how accumulation
     - Partnering value
     - Customer attachment/ trust
     - Scale and scope-driven transaction costs
     - Cycle time
     - Intellectual property advantages
     - Direct sales advantages
     - Channel advantages
     - Staff recruiting/ turnover advantages
     - Customer care
     - Service design quality
     - Regulatory/ legal advantages
     - Financial advantages
     - Standards development
   - Overall relative economic value

2. **Synergies with the Existing Businesses**
   - Financial synergies
   - Shared customers, networks, facilities, know-how
   - Brand recognition/reputation "capital"
   - Managerial skills
   - Purchasing economies
   - Technology synergies
   - Scale and scope economies, transactions costs
   - Economies in distribution/logistics costs

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3. **Defensive Value**
   - Deterrence / preemption of competitor entry to key markets
   - Prevention of scale / scope / first mover advantages
   - Ability to thwart competition

4. **"Learning" Value**
   - Experience, learning value, apart from immediate use
   - Improved access to new markets (apart from direct value)

5. **"Do-Ability"**
   - Organizational fit
   - Practicality (financial, know-how, management bandwidth, timing)

Especially in a situation where there is a plethora of options, and wide range of internal views regarding them, we've found that using such explicit criteria can help to achieve consensus.

V. PROJECT ORGANIZATION, TIMING, STAFFING, AND FEES

We propose to start this project as soon as possible, following your consideration and acceptance of this proposal. Our plan calls for a three month project, with progress reviews at least every three weeks. Once we get your feedback and approval for the broad outlines of this proposal, we can prepare a more detailed work plan.

Assuming that the scope described above is roughly right, and that you are ready to proceed, we have assembled a group of outstanding competitive strategy consultants and biomedical experts who are prepared to dive into this project and work with you over the next three-four months to get the right answers.

Staffing. This project team would be led by myself, Mr. Ed Resor, and Ms. Blanche Brann of Sag Harbor Group, supported by two distinguished experts, Dr. Samuel Waxman (M.D.), Professor of Medicine, Mount Sinai School of Medicine, and Dr. Donald Miller (M.D.), Professor of Epidemiology and Medicine, Boston University. As described in the biographical sketches and CVs in the Appendix, these consultants and specialists have outstanding track records and strong backgrounds in relevant disciplines – especially competitive strategy, Internet technology, software and database pricing/marketing, oncology, and biology. All their efforts on this project are of course subject to the terms of the non-disclosure agreement already in place between SHG and XYZCO.

Timeline. As noted, we have not yet completed a detailed work plan. However, at this point we estimate that this project would require a minimum of 12 weeks, with progress reviews every three weeks and a final review at the end. Our normal working arrangement is therefore a contract for a minimum of three months, renewable after that on a month-to-month basis.

If you have any questions, I am reachable day or night on my cell phone (516-721-1452) , or by email at Jhenry@sagharbor.com.

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Once again, we are extraordinarily excited about working with you and your team on this path-breaking project! Thanks for your patience.

Best regards,

_____

James S. Henry
Managing Director
Sag Harbor Group

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ATTACHMENT

Sag Harbor Group Profile and Team Biographies

December 2000

SHG OVERVIEW

Since 1992 the Sag Harbor Group has been helping its clients understand the intersection of technology and competitive strategy issues. It has served such leading clients as AT&T Solutions, A.B.B., A.T.Kearney, Business Design Associates, the Calvert Fund/Groupserv.com, Cemex, Celosis.com, CelticVision.com, ChinaTrust/the Koo Group, the F.B.I., Flooz.com, GE, General Motors, Global Wireless Holdings Ltd., GTE, Groupvine.com, I.BM., IBM/Lotus Development, Interwise.com, Lucent Technologies, Merrill Lynch, Monitor Company, PageNet do Brasil, PEOPLink.com, Polaroid, the Rockefeller Foundation, the Government of Spain (Extremadura), South Africa Telecom, the Swedish Government, TransAlta Utilities, Worknet Communications, and Volvo.

In the past 18 months, representative SHG client engagements have included:

- For a "leading global telecommunications company," a strategy for its "e-business solutions" unit; the valuation, deal negotiation, and M&A support for its acquisition of a $5 billion global Internet services businesses; an entry strategy for the DSL access business; and a design review for its effort to "e-enable" the provisioning/customer care provided to its 60 million customers.

- For a leading global wireless services provider, an assessment of strategy and technology options with respect to two-way wireless technologies in several key emerging markets, including Malaysia and China.

- For another leading wireless services provider, an assessment of strategy and technology options with respect to two – way wireless technologies and Internet services in Brazil.

- For a new .com in the e:commerce arena, an assessment of strategic and partnering options, and the development of a business plan for presentation to investors.

- For a leading Asian banking conglomerate, a review and critique of their retail Internet banking strategy

- For another .com in the group discussion area, a technology/development review, a suggested wireless strategy, and the development of a partnering strategy.

- For a third .com in the enterprise services provisioning arena, a review and critique of the proposed business model, and a series of partnering introductions/ discussions.

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- For a well-known leader in the "imaging technology" arena, a review of their existing strategic direction, strength, and weaknesses, and a proposed set of possible new business initiatives.

- For a leading world-wide management consulting firm, a strategy treatise on Internet banking and e-payments, for presentation to their top financial services clients.

- For a new technology leader in distance learning and Web-based collaboration, a competitive strategy, pricing, and positioning review.

In contrast to traditional consulting firms like McKinsey, Booz Allen, and Monitor, SHG focuses on "fast therapy," bringing a variety of outstanding, relatively experienced consultants to bear on strategy, operational, partnering, and investment decisions quickly, and in parallel. It also finds it valuable to combine deep knowledge of particular technical arenas like wireless technology, Internet security, e: payments systems, e:commerce, and middleware with a relentless focus on customer value, market segmentation, and insistence on clear competitive strategies.

SHG Team Leaders

- **JAMES S. HENRY**

Managing Director, Sag Harbor Group. Mr. Henry is a leading management consultant, with a special emphasis on competitive IT and wireless market strategy. He has served as VP Strategy, Lotus Development Corporation; Firm Economist, McKinsey & Company; and Manager, Business Development/ Chairman's Office, GE. He has managed projects on a wide variety of strategy issues for many prominent multinational companies. He is a founder of Instream, an electronic workflow company; Celtic Vision, a new cable network and Internet startup, and a founding partner of International Venture Partners, a direct equity investment firm based in San Paulo, Brazil.

Mr. Henry has written extensively about business and technology issues for leading publications. His articles have appeared in The New York Times, The Wall Street Journal, The New Republic, The Washington Post, U.S. News and World Report, Manhattan Inc., Harpers, The Washington Monthly, Fortune Magazine, Business Week, Newsweek, Time Magazine, The Tax Lawyer, International Development Report, Jornal do Brasil, The Manilla Chronicle, La Nacion, and El Financiero. He is also the author of several published non-fiction books and anthologies. His work has taken him to many emerging markets, including Bolivia, Botswana, Brazil, Chile, China, Colombia, Costa Rica, Egypt, Guatemala, Honduras, Malawi, Mexico, Namibia, Panama, Paraguay, the Philippines, Russia, the Sudan, South Africa, Tanzania, Zambia, the Sudan, Venezuela, and Zimbabwe. He is an honors graduate of Harvard College (B.A., Social Studies, Phi Beta Kappa), The Harvard Law School (J.D.), The Harvard Graduate School of Arts and Sciences (M.S. Economics), and a member of the New York Bar since 1978. He and his two children live in New York City and Sag Harbor, New York.

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- **ED RESOR**

Senior Consultant, Sag Harbor Group. Mr. Resor specializes in telecommunications project management and telecommunications strategy, and has implemented several large telecommunications projects. A 1974 graduate of Yale (B.A., Anthropology) and a 1980 graduate of the Yale School of Management (Masters), Mr. Resor worked as a management consultant with McKinsey & Co. in New York from 1980 to 1985, and then served as Sudan Country Director for Safe the Children from 1986 to 1990. Since then he has been focused on the problem of bringing appropriate telecommunications technology to developing countries, organizing a rural telecom development project in Eritrea, a bid for a nationwide cellular phone network in Haiti, and telecom companies in Somalia and Bangladesh. He has a detailed knowledge of the relevant wireless and Internet technologies, and a working knowledge of English, French, Arabic, and Dinka. Married, with three children, he lives in New York City.

- **BLANCHE BRANN**

Senior Consultant, Sag Harbor Group. For the past decade Blanche has specialized in strategy and business development with software, IT, and Internet technology companies. Most recently, as Director, Strategy and Alliances, AT&T Solutions, she focused on building alliances with key players in e:commerce, Internet design, and Internet infrastructure. Prior to joining AT&T Solutions, Blanche was a Solutions Alliance Manager for Advanced Network Services, later acquired by Worldcom, where she was in charge of relationships with many new Internet services companies.

- **DR. SAMUEL WAXMAN, M.D.**

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The Mount Sinai Medical Center
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New York, N. Y. l0029-6574
Phone:(212) 24l-7995/ (212) 289-2828

Current Academic and Professional Positions:

1997 Magnolia Award, Shanghai Municipal Government, Shanghai, China
1996 Honorary Professorship, Shanghai Second Medical University, Shanghai, China
1994-present Zena and Michael A. Wiener Professor of Medicine (Cancer), Division of Medical Oncology, Department of Medicine, Mount Sinai School of Medicine, N.Y. 10029
1992-present Consultant Professor, Shanghai Second Medical University , Shanghai, China
l972-present Head, Rochelle Belfer Chemotherapy Foundation Laboratory, Division of Medical Oncology, Mount Sinai Medical Center, New York, N.Y. l0029
l983-1994 Clinical Professor of Medicine; Department of Medicine; Mount Sinai School of Medicine, New York, N.Y. l0029

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l983-present Attending in Medicine; Department of Medicine; Mount Sinai Medical Center, New York, N.Y. l0029
l976-present Medical Director, Samuel Waxman Cancer Research Foundation, ll50 Fifth Avenue, New York, N.Y. l0l28

Biotech and pharmaceutical consultations and collaborations

Hoffman La Roche, Nutley, NJ
Merck Pharmaceuticals, Rahwah, NJ
Ligand Pharmaceuticals, CA
IDEC Pharmaceuticals, CA
Cell Therapeutics, Seattle
CelGene, New York
Ariad, Boston
Aronex, Houston
Intermune, CA

Educational Background

B.S.Cornell University, Ithaca, N.Y. 1953-l957
M.D.State University of New York,
Downstate Medical Center, Brooklyn, N.Y.l959-l963
(Summa Cum Laude)

Residency and Research Fellowships:

Intern The Mount Sinai Hospital, New York, N.Y. 1963-1964
Assistant Medical The Mount Sinai Hospital, New York, N.Y. l964-1965
Resident
Medical Resident The Mount Sinai Hospital, New York, N.Y. l965-l966
Research Fellow in The Mount Sinai Hospital, New York, N.Y. l966-l967
Hematology Research Fellow and The Mount Sinai Hospital, New York, N.Y. l967-l968
Chief Resident in Hematology

Academic and Professional Experience (l967-l983)

Assistant Instructor Department of Medicine; Mount Sinai l966- l967
in Medicine School of Medicine, New York, N.Y.
Instructor in Medicine Department of Medicine; Mount Sinai l967- l968
School of Medicine, New York, N.Y.
Associate in Medicine Department of Medicine, Mount Sinai
l969- l970
School of Medicine, New York, N.Y.
Assistant Clinical Department of Medicine, Mount Sinai l970- l974
Professor School of Medicine, New York, N.Y.
Associate Clinical Department of Medicine, Mount Sinai l974- l983
Professor of Medicine School of Medicine, New York, N.Y.
Assistant Attending The Mount Sinai Hospital l970- l974
Physician New York, N.Y.
Associate Attending The Mount Sinai Hospital l974- l983
Physician, New York, N.Y.
Attending Physician Veteran's Hospital970

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(Hematology)Bronx, N.Y.

Board Certifications:

Internal Medicine, 1970 Subspecialty Boards in Hematology, 1972

Professional Society and Organizational Membership:

Member, Subcommittee on Neoplasia, American Society of Hematology (1997-2001)
Member, International Affairs Committee of American Association for Cancer Research (1995-)
Associate Editor, Biological Regulators and Homeostatic Agents (1995-)
Editor, Molecular and Cellular Differentiation (1993-)
Editor, Differentiation (1991-)
Board of Directors, International Society of Differentiation (l988-)
Co-Organizer, International Conferences on Differentiation Therapy (1986-)
Member, American Society for Clinical Investigation
Medical Director, Samuel Waxman Cancer Research Foundation (1976-
Trustee, Leukemia Society of America, Inc. (l975-)
Member, Medical Advisory Board, Leukemia Society of America, Inc. (l975-)
Member, Subcommittee on Neoplasia, American Society of Hematology (l982-1996)
Member, Subcommittee on Nutritional Education, American Society of Clinical Nutrition (l983-l986)
Member, Subcommittee on Nutritional Anemias, American Society of Hematology (l976-l980)
Member, Alpha Omega Alpha
Member, Harvey Society
Member, American Society of Hematology
Fellow, American College of Physicians
Member, American Federation for Clinical Research
Member, American Society for Clinical Nutrition
Member, American Association for Cancer Research
Member, The International Society for Preventive Oncology

(Dr. Waxman's bibliography of 227 reviewed publications is available upon request)

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- **DR. DONALD R. MILLER**

Academic: Boston University School of Public Health
Office: CHQOER (Center for Health Quality, Outcomes, and Economic Research)
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Bedford, MA 01730 Boston, MA 02118-2394

EDUCATION:

Sc.D. in Epidemiology & Nutrition	1988	Harvard School of Public Health, Boston,
M.S. in Nutrition	1979	Harvard School of Public Health, Boston,
B.A. in Biology	1973	Reed College, Portland, OR

PROFESSIONAL POSITIONS:
Director and Epidemiologist since 1988
Epidemiology and Outcomes Services (EOS)/
Health Research Associates, Boston, MA
Senior Epidemiologist since 1990
Center for Health Quality, Outcomes, & Economic
Director of Database Development since 1998
Massachusetts Veterans Epidemiology Research and
Information Center (MAVERIC), Boston, MA
Associate Director of Research 1989-1992
Department of Medicine
University of Massachusetts School of Medicine
Epidemiologist 1980-1987
Slone/Drug Epidemiology Unit, Boston University

ACADEMIC POSITIONS:
Assistant Professor of Public Health since 1992
Depts. of Health Services; Social & Behavioral Medicine
Boston University School of Public Health, Boston, MA
Assistant Professor of Medicine since 1992
Department of Dermatology
Boston University School of Medicine, Boston, MA
Assistant Professor of Epidemiology 1989-1997
Preventive & Behavioral Medicine
& Medicine
University of Massachusetts School of Medicine
Instructor since 1989
Department of Health Sciences, Sargent College, Boston

TEACHING EXPERIENCE:
Course instruction in Nutritional Epidemiology, Clinical Epidemiology, and Nutrition at Boston University School of Public Health, Sargent College, University of Massachusetts School of Medicine, and Kushi Institute. Invited course lectures at numerous universities and professional society symposia.

PROFESSIONAL COMMITTEES:
Active committee participation including Diabetes Technical Advisory Group, Healthcare Analysis and Information Group, QUERI Cancer Initiative Working Group (VA), Colorectal

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Cancer Working Group, Skin Cancer Prevention Coalition (Mass. Dept. Public Health), Post-doctoral Training Advisory Comm., Curriculum Committee (BU), Boston Obesity Nutrition Research Center, Epidemiology Working Group.

RESEARCH SUPPORT:

Current grant support as principal investigator of over $2 million.

Selection of recent grants:`

Predictors of diabetes-related morbidity & mortality Bone loss in men: role of alcohol, depression, diet Genetic markers for bone density in men

Health related quality of life in veterans

Socioeconomic status and melanoma survival

Long-term health impact of body weight change

PUBLICATIONS:

Authorship of 16 book chapters and 96 peer-reviewed articles published in prestigious biomedical journals including New England Journal of Medicine, Journal of American Medical Association, Journal of Clinical Investigation, Journal of National Cancer Institute, and American Journal of Public Health.

PROFESSIONAL AFFILIATIONS AND CONSULTATIONS:

Membership in professional societies, including Soc. for Epidemiologic Research, American Society for Nutritional Sciences, Assoc. for Health Services Research, International Soc. for Pharmacoepidemiology. Serves as reviewer for several society journals. Provides research and scientific consultation to several independent investigators, professional societies, government agencies, and research businesses.

***

ENDNOTES

[1] This section and the preliminary conclusions in the following sections draw heavily on our interviews with you, Joe Brown, Glenna Burmer, and Mike Tippie, plus your September 2000 business plan , your August 2000 Management Report, and a variety of publicly-available industry information.

[2] As of October 2000, LS Bio had 82 staff, including 15 Ph Ds. CEO Brown, for example, a Ph.D. in Biochemistry from Cambridge, was formerly a VP at Bristol-Myers Squibb, in charge of Oncology Drug Discovery, and VP of Research at PathoGenesis Corp. before it was absorbed by Chiron. While at the Fred Hutchinson Cancer Research Center in Seattle in the 1980s, he pioneered development of the first monoclonal antibodies to cancer. CSO Dr. Burmer, an M.D. and PhD, was Director of New Pathogen Discovery for PathoGenesis Corp.

[3] Including 25 of the world's top 40 pharmaceutical companies.

[4] G Protein-Coupled Receptors, or 7-transmembrane receptors, bind extracellular ligands and transduce signals into cells by coupling to intracellular G-proteins. The GPCR family of receptors includes about 320 genes. They are the targets for about 50 percent of existing drugs, and the Human Genome Sequencing Project has also identified many more so-called "orphan" GPCRs that may be the targets for many more.

[5] See the article on this very subject in The Economist, December 9 2000, p.27.

[6] See the discussion of the continuing controversy about precisely how many human genes there are in Nature, June 2000. Companies like Incyte and Double Twist have estimated the number

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at over 100,000, but analysts like Green and Weissenbach, using a sampling technique that extrapolates from the number of genes in particular sequenced chromosomes, puts the number much lower, at 35,000.

[7] See the timely article in The Economist, December9 2000, 28-29. Scimagix has reportedly been working with Parke-Davis on automating the analysis of images produced by the technique gel electrophoresis. Oxford GyclcoSciences is also working on automating gel image analysis, and has also focused on automating time-of-flight mass spectroscopy. Millenium Predictive has focused on high-pressure liquid chromatography.

[8] Merck, for example, is reported to have only one pathologist on its internal staff. Other leading pharmaceutical companies have similar skill deficiencies.

[9] The conventional wisdom is that the top 20 protein families account for at least half of existing drug R&D.

[10] Ciphergen (2000).

[11] Standard estimates are that only one drug in three that reaches commercialization actually recovers its R&D investment. This statistic is often cited by the drug industry to justify its pricing behavior. As suggested here, another way to look at the matter might be to examine "cognitive" inefficiencies in current drug discovery methodologies.

[12] See Business Week, October 31 2000.

[13] DNA Sciences, for example, is focusing on establishing a "Gene Trust" with dna donations by way of blood samples from more than 4000 live donors.

[14] Oxford GlycoSciences received a US patent on May 16, 2000, for techniques related to its gel-based high-throughput imaging - "computer-assisted methods and apparatus for identification and characterization of biomolecules."

[15]See "The Global Application of Video Conferencing in Health Care," Odysseus Argy, MD., et. al. (www.americantelemed.org, Jan. 1999). See also A.K. Bhattacharyya, et. al, Case triage model for the practice of telepathology." Telemedicine Journal. 1(1): 9-17, 1995.

[16] Argy, supra. One of the first recorded instances of "telemedicine" occurred at the University of Nebraska as early as 1959, when a psychiatrist tried using conference calls for group therapy. In 1968, remote consultations were implemented at Logon Airport in Boston and physicians at MGH. In 1969, when X-ray images were sent across phone lines. But since 1997 there has been a dramatic increase in activity. For example, one estimate is that 60 percent of all spending on telemedicine by the US government to date has occurred since 1998. Andy Marsh, Euromed Project Manager, "The Creation of a Global Telemedical Information Society," October 2000. (http://www.hoise.com/vmw/analysis/euromedbuildingblocks/telemed.html).

[17] "Capitalization" refers to increases in capital/labor ratios for the profession as a whole.

[18] US patent 5216596 was issued to Corabi International Telemetrics, Inc., Alexandria, Va. on June 1 1993, covering a "telepathology diagnostic network." A subsequent related US patent, # 5297034, issued on March 22, 1994, explained the problem that the patented system was designed to solve as follows: "Pathologists are the physicians responsible for analyzing tissue and liquid specimens by light microscopy…Under current practice, specimens removed from a patient must be delivered to the pathologist who is to examine them. Under the best of circumstances, the examining pathologist works in a laboratory located at the hospital where the patient is. In such a case, the turnaround time can be short enough to allow the pathology diagnostic opinion to be rendered and the opinion to be acted upon during the same operation in which the specimen is removed from the patient. Naturally, being able to make and act on the pathology diagnostic opinion during a single operation is highly desirable. Alternatively, when the pathologist is not located at the same hospital, the specimens can be sent through the

mails or other means to a pathologist working at a diagnostic center at a distant location. This situation precludes removing the specimen and acting on the pathology diagnostic opinion during a single surgical procedure. This result not only adds to the cost of the treatment, but can also lead to adverse health effects inherent in delaying the therapeutic treatment and by subjecting the patient to multiple surgical procedures."

[19] This comment refers to the potential legal issues involved with "remote consulting" services by pathologists to practicing clinicians in the context of particular patients – for example, liability standards and local licensing requirements. It may be less relevant to the provision of remote services to drug companies. The absence of clear interstate regulatory regimes , including liability standards, licensing, and rules for insurance coverage and fee-sharing, is proving to be a significant obstacle to the deployment of clinical telemedicine, at least in the US. For example, at last count, at least 27 states and the District of Columbia have no interstate telemedicine licensing policies, (Telehealth Service Providers, Oregon, December 2000).

[20] These three companies use rather different techniques to produce quantities of human monoclonal (capable of targeting specific antigens) antibodies with the help of mice. To overcome the fact that mouse monoclonal antibodies are often rejected by the human immune system (the Human Anti-Mouse Antibody, or "HAMA" response), CAT has developed phage display and humanization techniques, genetically engineered and assembled from portions of mouse and human antibody gene fragments. Medarex also uses a variation on phage display and "humanized" mice. Abgenix uses what it calls in vivo affinity maturation, which takes much longer but, it claims, produces antibodies with higher affinities, greater specificity, and less costly manufacturing.

[21] One estimate is that CAT antibodies, for example, cost as little as $50 each, compared to the $2000/ four months figure cited for conventional rabbit-clone-based antibodies used by XYZCO.

[22] See the claims made by Medarex (www.medarex.com).

[23] While XYZCO's target gross margin for CRO projects is reported to be 70 percent, its actual recent average CRO performance is closer to 25 percent, and for projects involving ISH, less than 10 percent. XYZCO "Management Report," August 2000.

[24] XYZCO is not alone in pushing the introduction of new, higher-throughput techniques in molecular biology. See, for example, Albert Heal, "Molecular Biology Automation in the Clinical Laboratory," Journal of Clinical Ligand Assay, Spring, 2000.

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