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A Final Report for:
**COMPACT GAMMA-RAY IMAGER FOR IN-VIVO
GENE IMAGING**

Submitted under:
Contract No. DE-FG02-99ER82892

Submitted to:
**Chicago Operations Office, Contracts Division
9800 South Cass Avenue
Argonne, IL 60439**

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ABSTRACT

Alternative surfaces for industrial and medical components are sought to increase durability and life. In many cases, attempts by researchers to coat diamond or ceramics onto metallic components, such as earth drilling equipment, have failed to produce a practical solution, due to poor adherence of dissimilar materials and brittleness of the films. Increasing hardness and strength of single layer structures are concomitant with decreasing toughness, ductility and adherence.

Phase I demonstrated for the first time fabrication of functionally graded, Ti/TiN/TiBN nanocrystalline multiphase (TiN, TiB₂ and BN) coatings with a hardness > 42 GPa. The graded structure provided a gradual transition from metallic to covalent bonding through the thickness of the film, enhancing adhesion. Wear resistance evaluation (pin-on-disk) for 5 million cycles (25 days) at 1 GPa contact stress showed no wear, indicating the potential for the coating to extend the lifetime of substrate materials by several orders of magnitude.

The objective of Phase II will be fabrication and optimization of nanocrystalline multiphase (Ti-B-C-N) graded layer structures. Effort will be devoted to precisely controlling the ratios between the various film constituents (TiN, TiB₂, B₄C, BN) and relating them to adhesion, internal stress, hardness and wear resistance. Our coating will be deposited on earth drilling components and will be evaluated at Spire and by our commercial partner for incorporation into their products

Abstract

A compact, low-cost, gamma-ray imaging system is needed to study gene expression in small animals. State-of-the art electronic imaging systems have insufficient resolution and animals must be sacrificed for detailed imaging that precludes time evolution studies. With improved electronics radioactive tracers attached to gene markers can be used to track the absorption and mobility of gene therapy medications in live animals. Other instrumentation being developed for medical applications does not have the response to match the radiation source for this work.

The objective of this research was to develop thick film (Cd,Zn)Te detectors matched to the gamma ray energy of ^{129}I . The detector would be a direct readout device using p-i-n diodes formed from the high Z material absorbing the radiation, with separate readout. Higher quality semiconducting material was expected from epitaxial growth on GaAs, a near lattice matched substrate. In practice, it was difficult to obtain material with high resistance and low leakage current.

Spire Corporation achieved the goal of fabricating working detectors in (Cd,Zn)Te deposited on GaAs. The spectra of an alpha emitter (^{225}Am) was adequately resolved in thin film devices. Thick p-i-n diodes were fabricated but other processing problems prevented full demonstration of a gamma ray detector.

1. INTRODUCTION

A central focus of molecular biology is the understanding of the impact of genetic expression on cellular growth, differentiation, and function. Currently, only *in vitro* techniques are readily available for the study of gene expression and regulation. *In vitro* studies have the serious drawback that they permit measurement of relevant distributions or concentrations at only a single stage in the expression process, since the animal must be sacrificed to make the measurement. Hence dynamic information or data regarding the time progression of longer term processes such as the effects of gene therapy, are unobtainable. There is thus a pressing need for techniques to permit real-time, *in vivo* studies of gene expression.

Antisense oligonucleotides can be labeled with any of a number of radioisotopes, thereby correlating isotope concentration with messenger RNA transcription. Dewanjee *et al.* have utilized such radiolabeled probes along with conventional gamma cameras for noninvasive imaging of c-myc oncogene mRNA in breast cancer research.¹ Measuring the presence of enzymes resulting from the expression of a transduced gene can monitor efficacy of gene therapy. Tjuvajev *et al.* have recently employed radiolabeled marker substrates for imaging herpes virus thymidine kinase gene expression. For this study, a dual-head clinical gamma camera was used.

A particularly promising radioisotope for use in small animal genetic studies is ^{125}I . ^{125}I decays via electron capture (half life ~60 days) to a metastable state of ^{125}Te , followed by emission of a 35 keV gamma-ray and several characteristic X-rays (27-32 keV). It is commercially available linked to nucleic acids and antibodies. Although the relatively low gamma- and X-ray energy would result in higher than optimal absorption in humans, ^{125}I is ideally suited for animal imaging. Furthermore, coincidence imaging of the gamma- and X-rays permits background rejection, thereby potentially permitting detection of extremely low concentrations.

Although these techniques hold great promise, current gamma cameras are not well-suited for small animal imaging because of their relatively poor spatial resolution (3-5 mm FWHM at best). Many studies using mouse models could benefit significantly if a gamma camera with spatial resolution of the order of 1 to 2 mm were available. It was the purpose of this project to develop such a device.

Pixellated semiconductor detectors are attractive for these applications since they offer not only the possibility of higher spatial resolution, but also better energy resolution than scintillator-based detectors, allowing for better rejection of scattered photons. Cd(Zn)Te (CZT) detectors are the preferred option since they offer direct detection, high stopping power, good energy resolution, and room temperature operation. Several groups have demonstrated gamma-ray imaging using CdZnTe detector arrays.

Present CZT based gamma cameras are very expensive. Currently, CdZnTe is grown by the high-pressure Bridgman (HPB) method. Though this method offers large-area crystals, two issues, material non-uniformity over large areas and high cost, currently limit their potential for large commercial application. The material non-uniformity limits the size of the detector arrays

to 1-inch, and several detector arrays are tiled together to construct large-area imagers. Typically, 1 to 2 mm thick CdZnTe detectors are used for imaging.

The overall objective of this project, not funded to completion, was to build a low-cost, high performance, large-area CdZnTe gamma camera fabricated using CdZnTe layers grown by metalorganic chemical vapor deposition (MOCVD) for gene imaging studies in small animals. Since ^{125}I is commonly used for laboratory imaging applications and the emitted gamma ray energy is only 35 keV, CdZnTe layers with thickness of the order of 200 to 300 μm are sufficient to have 100% stopping efficiency. The technical approach was to grow single crystal CdZnTe layers with thickness of the order of 200 to 300 μm by MOCVD. MOCVD offers high material uniformity over large areas and high growth rate (15 $\mu\text{m/hr}$), hence there is no need for tiling several detectors to build a large-area imager. For laboratory animal studies, a 6 cm x 6 cm area imager is sufficient, and we propose to deposit CdZnTe on 3-inch GaAs substrates.

Background on In Vivo Imaging - At present, *in situ* hybridization and immunochemical assays are the only methods available to follow gene expression and regulation *in situ*. There is a need to detect gene expression *in vivo* for an extended period of time for an organism. The imaging technique should be real-time, quantitative, and able to follow an organism over several days.

Current Technology for Imaging - Presently there are only two direct means of imaging gene expression and regulation *in vivo*. One method uses green fluorescent protein (GFP) fused to a gene promoter of interest, but the GFP method only works for transparent animals. The second method relies on the fact that when the information stored in the sequence of DNA of a gene is expressed, it is transcribed into an mRNA transcript which is then translated into a protein.

Recent Research - Recently, Dewanjee *et al.* have shown that it is possible to construct and successfully use radiolabeled anti-sense RNA probes to detect target mRNA *in vivo* in laboratory animals using a standard gamma camera as the detector system.¹ They used a gamma camera which produced scintiphotographs with spatial resolution of the order 5 mm. They demonstrated that the antisense probe could be used for noninvasive imaging of c-myc oncogene mRNA for malignant tumors. Many researchers have used standard gamma cameras to image monoclonal antibodies with radiopharmaceutical markers. Current gamma cameras have spatial resolution of the order of 3 to 5 mm. Clearly, higher spatial resolution suited for the above applications is needed.

Toward this goal, a group from Thomas Jefferson National Accelerator facility (TJNAF) is currently developing a high resolution gamma-ray imager with suitable spatial resolution to image gene expression in live mice. They use radioisotope iodine 125 (^{125}I) as the probe and utilize crystal scintillators and a position sensitive photomultiplier tube. ^{125}I decays via electron capture emitting a 35 keV gamma-ray with the prompt emission of several 27-32 keV $K\alpha$ and $K\beta$ shell X-rays. Because of this advantage, they used a coincidence detection scheme to reduce the background radiation contribution to the image. Mouse imaging studies of iodine uptake by the thyroid and melatonin receptor binding have been done with this detector system using low

doses of ^{125}I . Their studies clearly demonstrated that a high resolution gamma imager will be useful for gene expression studies however, they were only able to achieve spatial resolution of 3.5 mm due to their detector design. They used scintillators coupled to photomultiplier tubes for imaging. Since scintillator has energy resolution of the order of 10%, decreasing the spatial resolution further by using collimators will reduce the sensitivity.

In nuclear-medicine, a gamma-ray emitting radiotracer is injected into the body and the resulting biodistribution is used to observe tumors, lesions and blood flow. Current gamma cameras typically use large flat scintillators and multiple photomultiplier tubes to deduce interaction locations using Anger-style logic. The intrinsic spatial resolution of these detectors is a few mm FWHM. The *overall* system spatial resolution is generally limited by the collimator, whether it be a parallel hole or pinhole design. There is a trade off between increasing the overall spatial resolution of camera and its sensitivity such that increasing collimator spatial resolution from 10 mm FWHM to 5 mm reduces the sensitivity by a factor of 4. Increasing the length of the collimator will improve the spatial resolution, but the detector will remain the limiting factor. In these detector systems, gamma-rays are absorbed in a scintillator and generate optical photons. A fraction of the photons are then emitted into a photomultiplier tube where they generate a proportional output signal. Even though the scintillator can have a high detection efficiency (90 to 95%), the resulting energy resolution of the whole system is less than optimal due to the poor conversion of absorbed quanta to electrical signals. This poor conversion efficiency is caused by low light output of the scintillators, optical losses due to geometry, absorption losses due to coupling, and losses at the photomultiplier interface.

The image spatial limitation can be overcome by pixellated detectors with resolutions less than 1 mm used in one of several innovative SPECT camera designs. An example is the use of a multiple pinhole collimator being used in the design of a high resolution brain imager at the University of Arizona.² The increased sensitivity afforded by the pinhole geometry could be traded to improve spatial resolution. This is important as tumors are often heterogeneous, and just as partial volume sampling compromises image quantitation, it also limits the researcher's ability to optimally sample and microscopically characterize the tissue of interest. Since tumor size is an important prognostic indicator there is strong motivation to detect malignancy at the earliest possible stage when they are less than 5 mm. Improvements in energy resolution improve image contrast and spatial resolution by reducing the scattered gamma-rays in the image.

CdZnTe Detector Technology - Cadmium zinc telluride (CdZnTe) has been shown to be an excellent material for spectroscopy of X- and gamma-radiation. It has particularly good sensitivity for the photons emitted by ^{125}I , since the K absorption edges for Cd and Te, at 26.7 and 31.8 keV, are just below the photon energies of interest. The wide band gap of CdZnTe gives it low dark current at room temperature, and therefore low noise. The long electron drift length (up to several cm) provides good charge collection efficiency, which is a prerequisite for high spectral resolution.

Most applications of CdZnTe for X-ray or gamma-ray imaging and spectroscopy involve bulk crystals grown by the high-pressure Bridgman method. Although this material has excellent properties for spectroscopy of hard X-rays (>100 keV), it has several drawbacks. The key problem is that the yield of high-quality material is low, causing the cost of spectrometer-grade

detectors to be prohibitive. Furthermore, structural defects and grain boundaries limit the maximum useable area of a single detector to about 2 cm², so that many small detectors must be tiled to form an imaging array.

While the use of crystals several millimeters thick is unavoidable for detection of radiation above 100 keV, at low energies most of the bulk detector volume is wasted, since the majority of photons are absorbed within 100 μ m or so. For example, a 100 μ m-thick Cd_{0.9}Zn_{0.1}Te film would absorb over 80 % of incident photons at 35 keV. A Cd_{0.9}Zn_{0.1}Te epitaxial film of this thickness is an efficient alternative to bulk crystals for producing large-area detectors for radiation in the 10-50 keV range.

Technical Approach - The overall objective of this work is to develop a compact, high resolution gamma-ray imager (10 cm x 10 cm) for gene expression studies using CdZnTe thin-film detectors. The CdZnTe films would be grown on semi-insulating GaAs substrates by metalorganic chemical vapor deposition (MOCVD). The devices would use an orthogonal strip geometry, which allows the GaAs substrate to be left in place to provide a more rugged device. This approach reduces the complexity of the electronics and avoid the expense of bump bonding. n-type strips will be fabricated in the SI-GaAs wafer by diffusion or ion implantation, and p-type strips will be fabricated on top of the CdZnTe film by thermal evaporation of CdTe and lift-off. This PIN structure will deplete the CdZnTe film and allow relatively low-resistivity films to be used. Figure 1 shows the proposed camera concept.

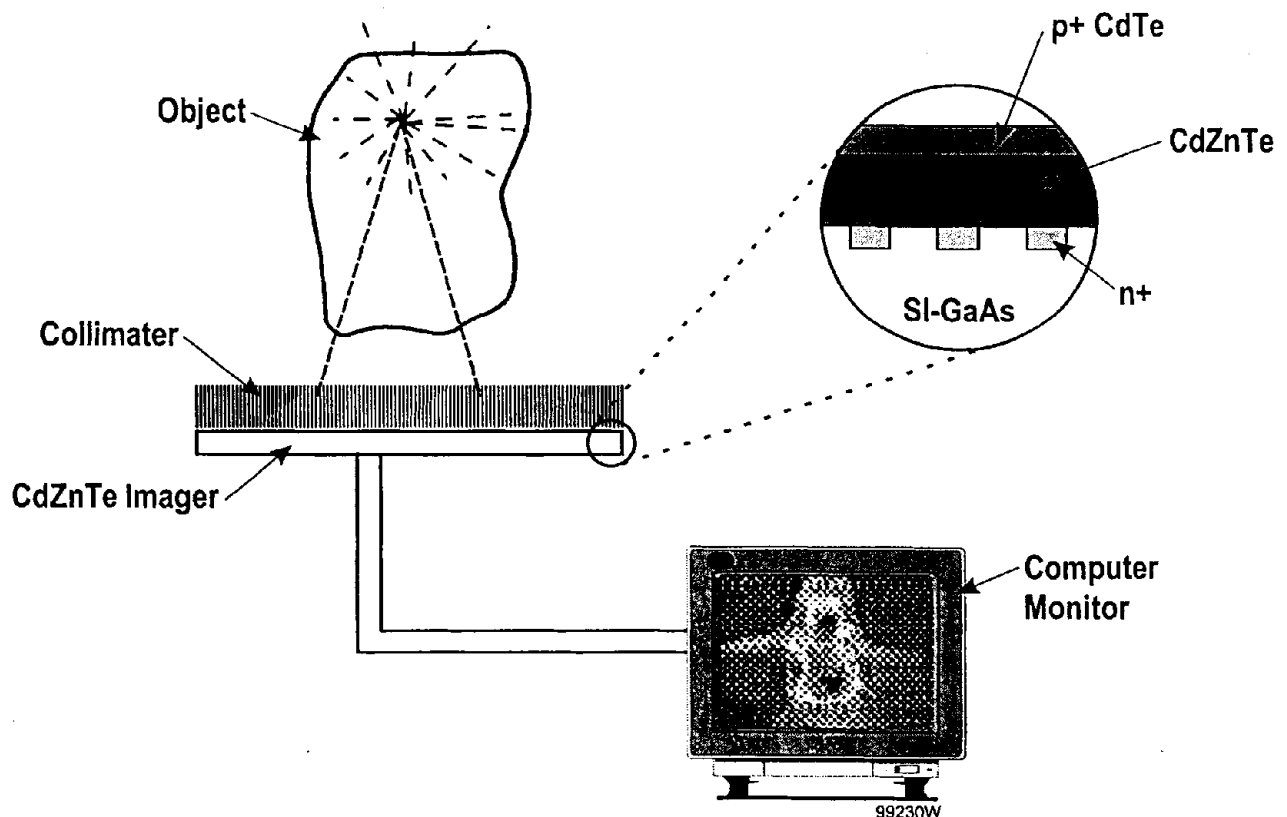


Figure 1 Concept diagram.

2. TECHNICAL OBJECTIVE OF THIS PHASE I RESEARCH PROJECT

The objective of this phase of the research was to deposit a thick layer (preferably 0.100 mm) of (Cd,Zn)Te on GaAs and show that the electrical properties of this layer are sufficient to fabricate the desired detector.

3. EXPERIMENTAL PROCEDURE AND RESULTS

Prior to the start of this research, Spire had experience with deposition of II-VI materials. The following parameters were fixed by this previous work:

- choice of source metal-organic compounds
- temperature of source materials
- total gas flow into the reactor and total pressure
- preheat cycle
- nucleation step

Source compounds were dimethylcadmium, dimethyltelluride, and diethylzinc. Choices were based on physical parameters needed for the MOCVD process including melting point, boiling point, vapor pressure at room temperature, and stability. All of these compounds have a melting point below 0°C so that they are liquid for typical operating conditions. The boiling points for these compounds are above 90°C and they are stable for long periods in the liquid phase. They are also stable in the vapor phase at lower temperatures. The vapor pressure at ice point (0°C) are, respectively, 3.5, 10, and about 14 torr.

The last two variables determine deposition uniformity based on known flow patterns for a (mostly) hydrogen gas stream. Other process parameters were also fixed, for example, the substrates were always preheated, typically for a minimum of ten minutes and most often for 20 minutes. This step occurs at a temperature of 625°C and removes any residual trace of organic contaminants. During this preheat cycle, the carrier gas flow is established in the transport lines. This preliminary flow gives time for equilibration, especially at low flow rates. Another fixed process parameter is the "nucleation" step.

Experiments were conducted to test the effect of the following variables on deposited films to optimize the metalorganic chemical vapor deposition (MOCVD) process: prebake time and temperature, deposition temperature, ratio of group II compounds to group VI compounds (Te), ratio of zinc to cadmium, and the effect of counter doping with phosphorus. The total flow rate into the reactor (5 slpm) and the pressure (500 torr) were fixed. The carrier gas and diluent was always hydrogen. Parameters are shown in Table 1. A diagram of the apparatus is shown in Figure 2.

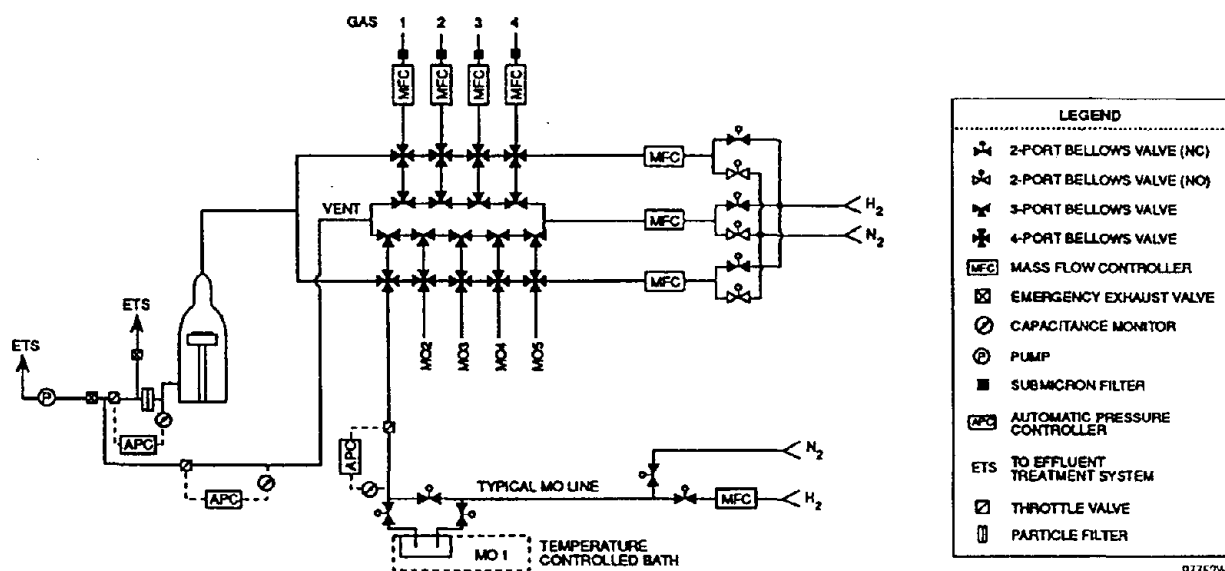


Figure 2 Schematic of MOCVD reactor.

At the bottom of Figure 2, labeled typical MO line, is the gas flow through a typical metal organic source. There is such a source for each of Cd, Zn, and Te. The source chemical was kept in a "bubbler" at a fixed temperature (reported above) that maintained the source as a liquid at high vapor pressure (few torr). The carrier gas, flow rate given in Table 1, was fed into this source liquid as a stream of bubbles, hence the name for the apparatus, "bubbler". Above the surface of the source liquid was a region of vapor kept in equilibrium at a fixed (and measured) pressure of 750 torr. The mount of source material fed into the reaction chamber was a function of the vapor pressure of the source liquid, pressure in the bubbler, and carrier flow rate. Each of these variables was controlled, the vapor pressure of the liquid being a function of the temperature.

The parameters given in Table 1 are for the reaction chamber, shown in Figure 3. The overall pressure for this reaction chamber was maintained at 500 torr. The temperature of the chamber and its variations are shown in the table. Temperature was measured by a thermocouple (not shown) placed inside the rotating rod which extended up into a recess in the susceptor. The thermocouple did not rotate. The surface of the substrate material would typically be a few degrees lower than this measured temperature, and it might also vary with type of substrate material. The total gas flow into this chamber was 5 liters per minute. All of this flow, but the metalorganic vapors from the bubblers, was hydrogen.

As shown in Table 1, initial experiments deposited CdTe films. These films did not have smooth surfaces. Although the Hall mobility of the films was higher than the mobility of ZnTe films, function x-ray detectors could not be fabricated on these samples. The best crystal structure (low FWHM of peak x-ray rocking curve), surface finish, resistivity and mobility combination was found for ZnTe films grown at high temperature (475°C), with greatest excess of tellurium (high VI-II ratio). Results are summarized in Table 2.

Table 1 CVD test run parameters.

run M8	bake Temp deg C	bake time sec	nucl temp deg C	nucl time sec	dep temp deg C	dep time sec	DMCd sccm	DATE sccm	DEZn sccm	press torr	Phos Doping
145	600	600	440	20	440	7200	75	150	0	500	
146	625	600	675	20	675	1800	75	150	0	?	
147	625	600	475	20	475	1800	75	150	0	500	
148	625	600	475	20	475	1800	75	360	0	500	
149	625	1200	475	20	475	1800	75	500	0	500	
	clean	chamber	between	runs							
150	625	1200	475	20	475	3600	0	200	170	500	
151	625	1200	525	20	525	3600	0	200	170	500	
152	625	1200	420	20	420	3600	0	200	170	500	
153	625	1200	420	20	420	3600	0	200	170	500	
154	625	1200	475	20	475	3600	0	400	170	500	
155	625	1200	475	20	475	3600	0	200	170	500	
156	625	1200	475	20	475	3600	0	500	170	500	
157	625	1200	450	20	450	3600	0	500	170	500	
158	625	1200	500	20	500	3600	0	500	170	500	
159	625	1200	485	20	485	3600	0	500	170	500	
160	625	1200	475	20	475	3600	0	500	170	500	
161	625	1200	475	20	475	900	0	500	170	500	
162	625	1200	475	20	475	3600	0	500	170	500	
163	625	1200	475	20	475	3600	0	500	170	500	
164	625	1200	475	20	475	3600	0	500	170	500	25/1/25
165	625	1200	475	20	475	3600	0	500	170	500	75/1/60
166	625	1200	475	20	475	3600	0	500	170	500	100/1/60
167	625	1200	475	20	475	900	0	500	170	500	100/1/180
168	625	1200	475	20	475	4500	0	500	170	500	100/1/180
169	625	1200	475	20	475	3600	75	360	0	500	
170	625	1200	475	20	475	3600	0	500	170	500	
171	475	600	475	20	475	1800	0	500	170	500	
172	625	1200	475	20	475	1800	0	500	170	500	
173	625	1200	475	20	475	10800	0	500	170	500	
174	625	1200	475	20	475	7200	0	500	170	500	

Table 2 Sample data analyses.

Run m8	Thickness microns	VI:II ratio	dark I nA	At volts	Notes	X-ray (arcsec)	Hall cm ² /v/sec
145	26				not smooth surface	FWHM	
146	0						
147	4.8						
148	7.3	6.9					600
149	7.1						720
150	7.8						
151							
152							
153			13	-10	#1 ZnTe/n+GaAs	386	
154		4	2.7	-20	#1 ZnTe/n+GaAs		
			short		#3		
			105	-1	#2		
155	11	8	1.9	-10	#1	338	
			0.7	-4	#2		
			192	-5	#3		
156	15		13	-7		78	
			150	-8	#4		
			60	-7.2	#2 22V dark/37V alpha		
			12	-8	#2		
			22	-7.2	#3		
			265	-8	#3		
157							
158							
159							
160	1.5					3095	
161	1.5				source run out	very	smooth
162	13					367	
163	rep. 162						
164							
165							
166	3						82
167							62
168			200	-2	#1 pZnTe/i-ZnTe/nGaAs		
			>1000	-1	#2 ditto		
			>7,000	-2	#3 ditto		
169	rep. 148	6.9			surface very shiny		709
170	rep. 156	10	4.7	-10	#3 ZnTe/p+GaAs	460	
			71		nice alpha peaks at 50 volts		
	surface	shiny on	GaAs		surface hazy on GaSb		
171					cross-section micrograph	340	
						957	
172					surface shiny		
173						85	
174					very good surface		

Notes:

#1 conductive rubber contact

#2 In Solder contact

#3 AuCl contact

#4 Au and In contacts on top

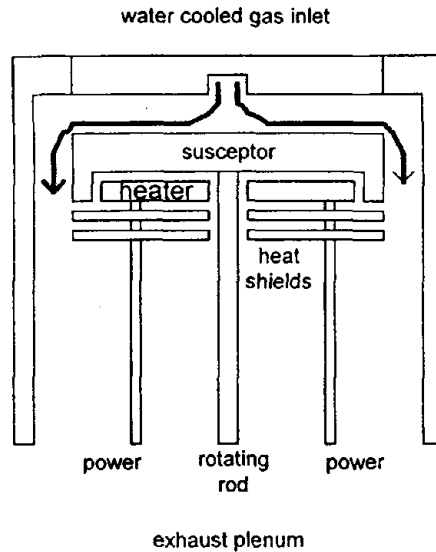


Figure 3 Cross-section diagram of Spire designed close-spaced MOCVD reactor for improved uniformity.

A double crystal X-ray diffractometer was used to obtain high accuracy data showing the peak width for x-rays diffracted by deposited films. In Figure 4, the polycrystalline peak (left) has a half-width of about 1,000 arc-seconds. The epitaxial film has a peak width less than 100 arc-seconds, comparable to that of the substrate. Only ZnTe films deposited on top of GaAs at a temperature of at least 475°C showed the preferred structure (Table 2).

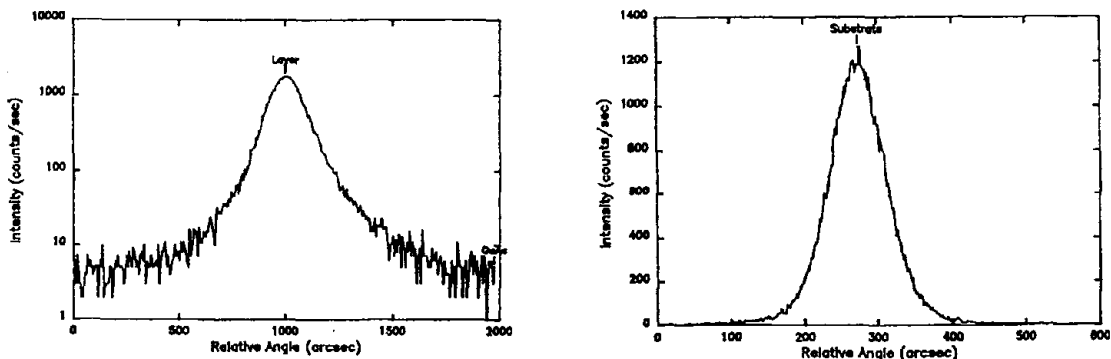


Figure 4 High accuracy x-ray diffraction scan from polycrystalline ZnTe on GaAs (left) and from epitaxial film (right)

Radiation detector diodes were fabricated according to two schemes, shown in Figure 5. In one case, we attempted to fabricate a p-i-n diode by sandwiching a high resistivity film (intrinsically doped) of ZnTe between highly doped GaAs. In the second case we fabricated Schottky diodes with AuCl contacts directly on top of the same ZnTe film. All devices from the GaAs sandwich illustrated ohmic behavior without diode properties. We believe that better contact procedures need to be developed for this device. The other diodes were good, typical current - voltage curves are shown in Figure 6.

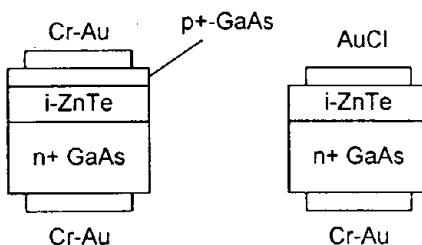


Figure 5 Diagram of diodes fabricated to demonstrate detector function (not to scale) N+ GaAs substrate was about 200 microns thick, the ZnTe film was 30 microns thick, and the cap was only 1 micron thick. Metal layers were sub-micron thickness.

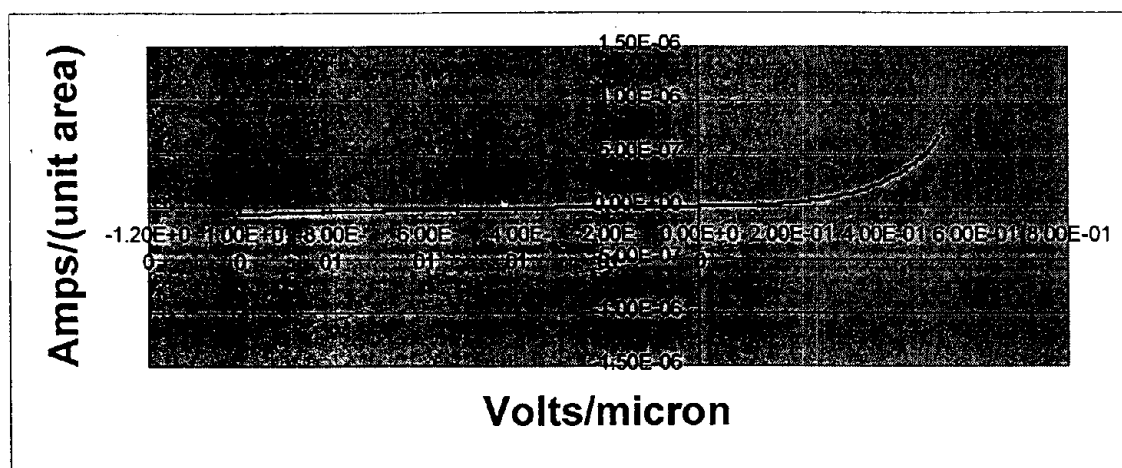


Figure 6 Current – voltage plot of AuCl Schottky barrier diodes in dark and light (higher current) conditions. Leakage current at low voltage is under 20 nA.

The P-I-N diode was tested as a radiation detector to show feasibility of the project. Because this preliminary device was very thin, an energy spectrum from ^{241}Am alpha source was captured (Figure 7).

4. CONCLUSIONS

For the facilities used, we found that thick semiconductor films with high resistance could only be deposited for compositions with no cadmium present. ZnTe material was successfully fabricated into p-i-n devices with low leakage current, the latter characteristic being strongly dependent upon metallization scheme. For thinner films, the energy spectra of ^{225}Am was resolved.

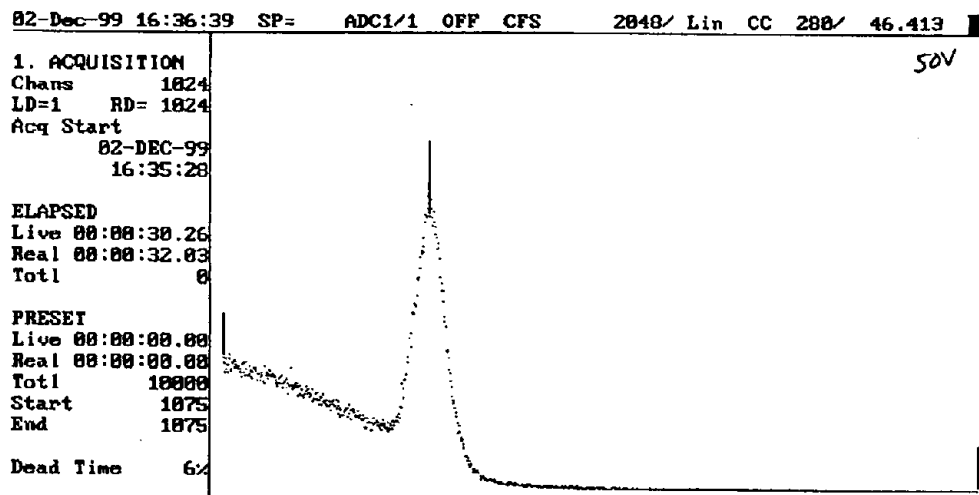


Figure 7 Energy spectrum from ^{241}Am alpha source resolved by PiN diode detector of ZnTe deposited on top of GaAs by MOCVD.

5. RECOMMENDATIONS

Real time gene expression can be imaged by other techniques, such as MRI.³ However, high resolution solid-state radiation detectors offer lower cost and ease of use in the laboratory. Chemical vapor deposition (CVD) of (Cd,Zn)Te on top of silicon CCD readout would combine the innovative technology developed by this research with low-cost, practical engineering solutions. Continued funding for this development would give the researchers the tools they need while also improving products available for medical applications.

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