Valirx
Bioscience Innovation

GENEICE PLATFORM

GENEICE INTRODUCTION

GENEICE-INTRO

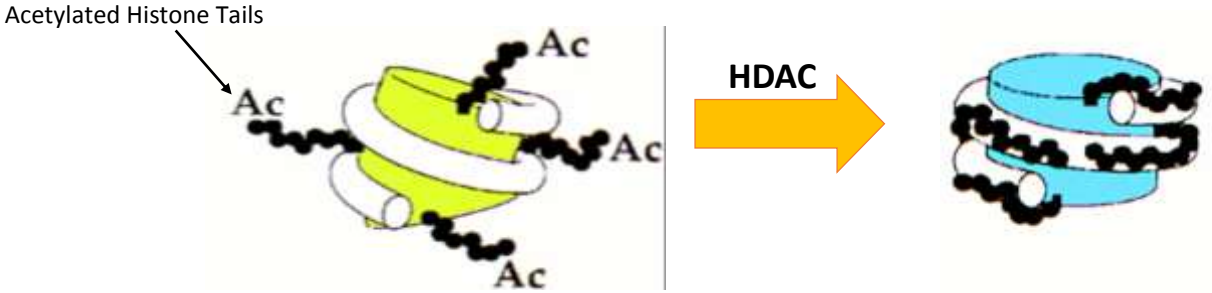
- GeneICE™: Gene Inactivation by Chromatin Engineering – "Silencing of Rebellious Genes"
  - Patents granted in Europe, US and Australia

- Therapeutics and discovery platform
  - GeneICE™ recruits and applies gene silencing complexes known as Histone Deacetylase Complexes (HDACs) to target genes involved in cancer, effectively "switching off" genes involved in certain forms of cancer

MOA-1

GENEICE CELLUAR MECHANISM

A cellular mechanism for long term gene repression

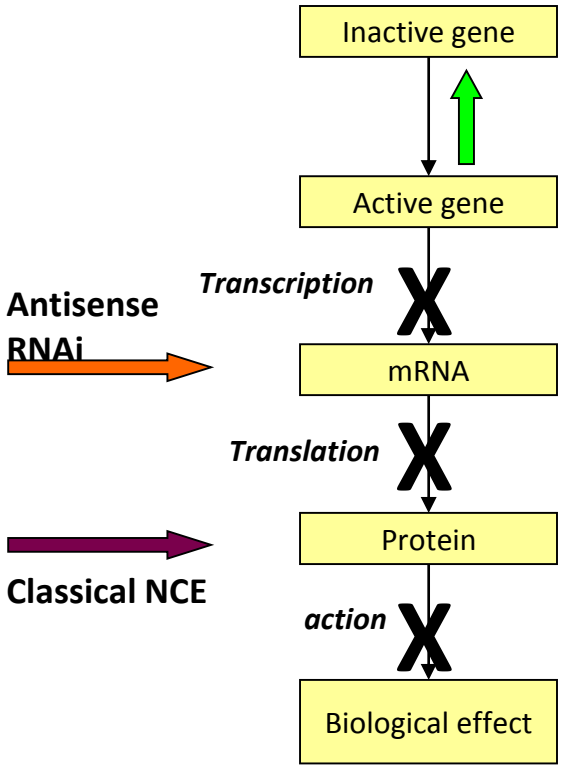


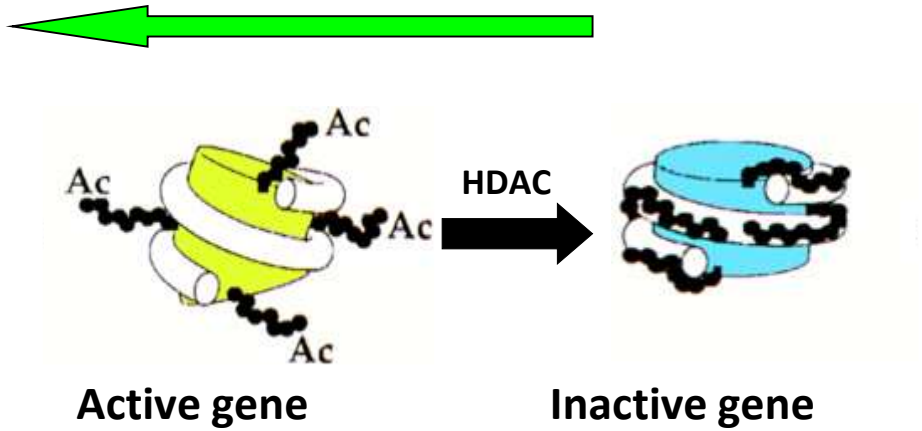
Active gene
(accessible to transcription factors)

Inactive gene
(inaccessible)

GENEICE MECHANISM

MOA-2

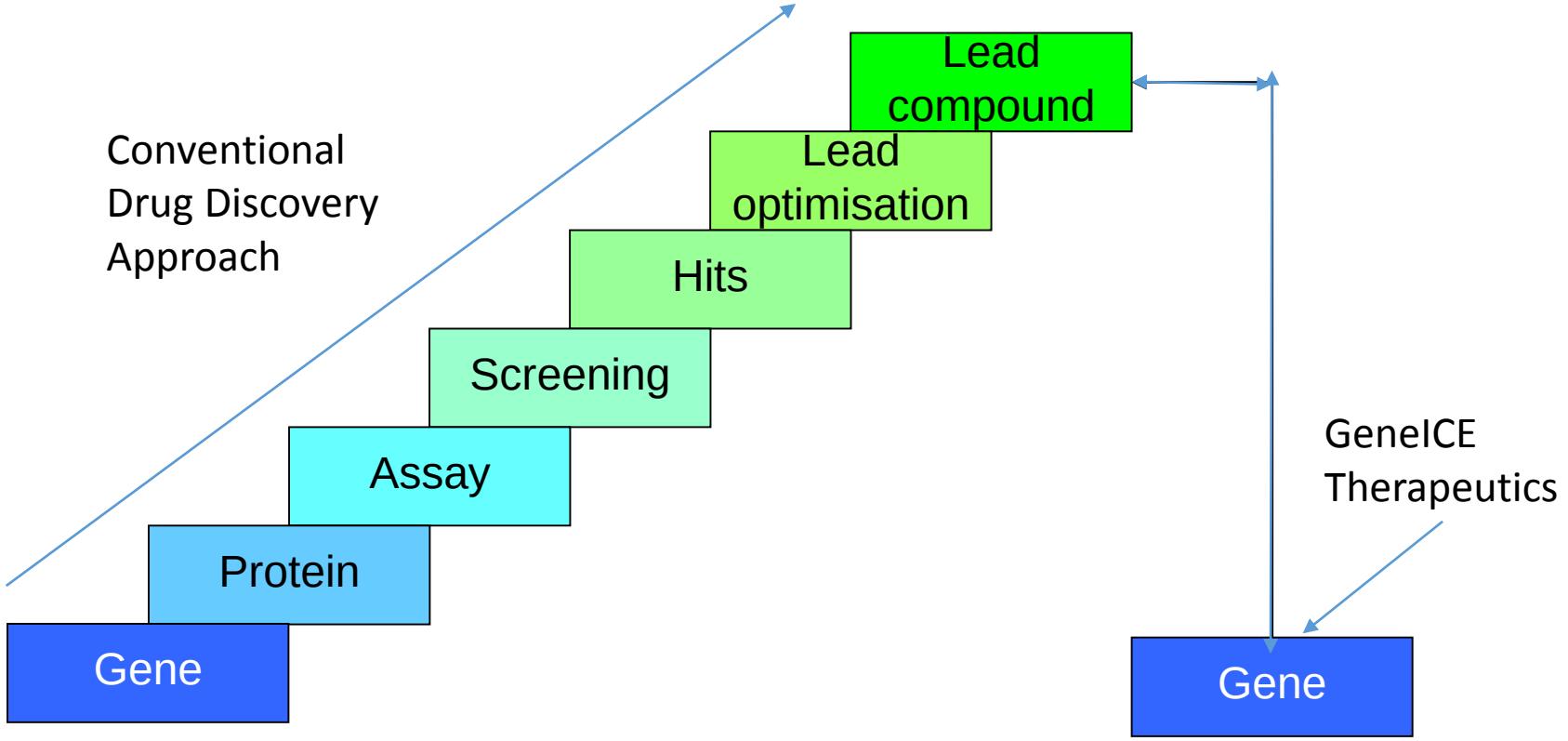




GeneICE Molecule acts upstream and prevents transcription.

GENE TO DRUG

Gene to Drug



GeneICE THERAPEUTICS

Comparison

Comparison with conventional drug discovery

GeneICE Drug Discovery	NCE Drug Discovery
❑ Genomic Target	❑ Protein Target
❑ Proof of gene silencing confirms that target is suitable for therapeutic intervention	❑ Typically 9 out of 10 protein drug targets prove to be intractable
❑ Each gene silencing construct is a potential drug. Constructs can be produced in ~2 weeks	❑ Conventional medicinal chemistry approach is lengthy and has low hit rate
❑ Therapeutic molecules offer high target specificity and low dosage, thereby reducing the potential for toxicity	❑ Failure rate in development is ~80%

GENEICE STRUCTURE

Structure

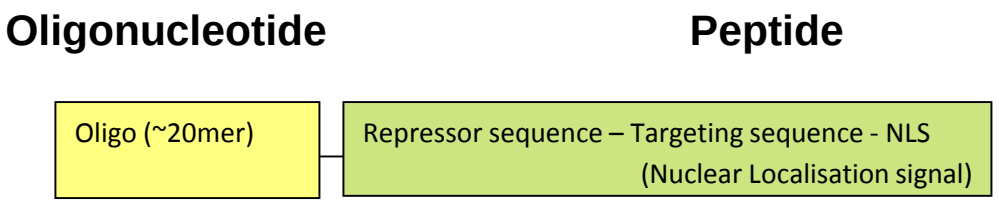
Valirx is developing novel GeneICE drugs based on this principle.

The first of these is a GeneICE drug targeted to suppress bcl-2 production of tumours cells leading to apoptosis.

- a sequence specific DNA binding Oligonucleotide that binds selectively to the gene of interest.
- This can be targeted to the gene promoter, the transcription start site or elsewhere in the primary transcript.
- a gene activity repression peptide that recruits HDAC to the gene.

Design of GeneICE molecules: GeneICE constructs are oligonucleotide-peptide conjugates (MW ~11,000)

The overall design is:



GeneICE RESULTS

GeneICE

- The following summarise the findings of a series of studies made using tumour models using a dose range of GeneICE anti BCL2 compared various controls.

- In each experiment the compounds were given to the models at day zero and at each time point a significant selection of the models for each treatment were measured for tumour growth *post mortem.*

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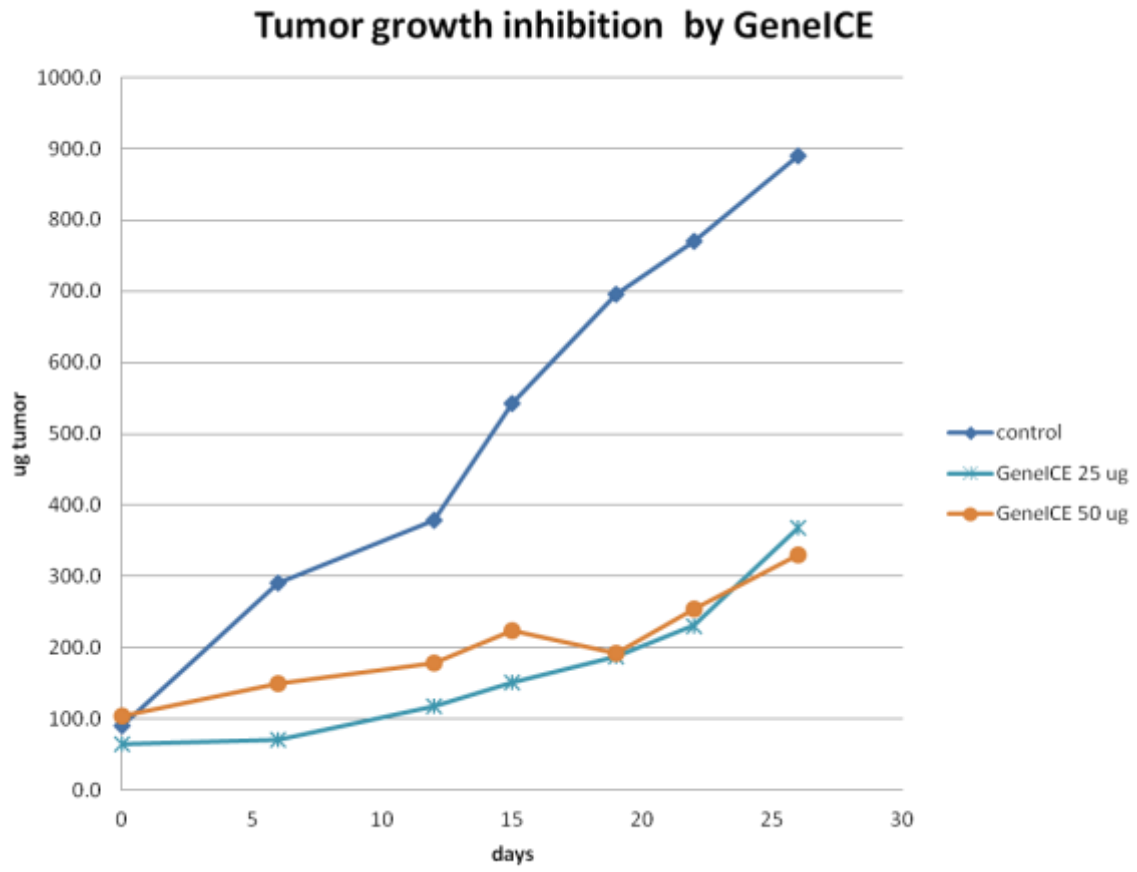
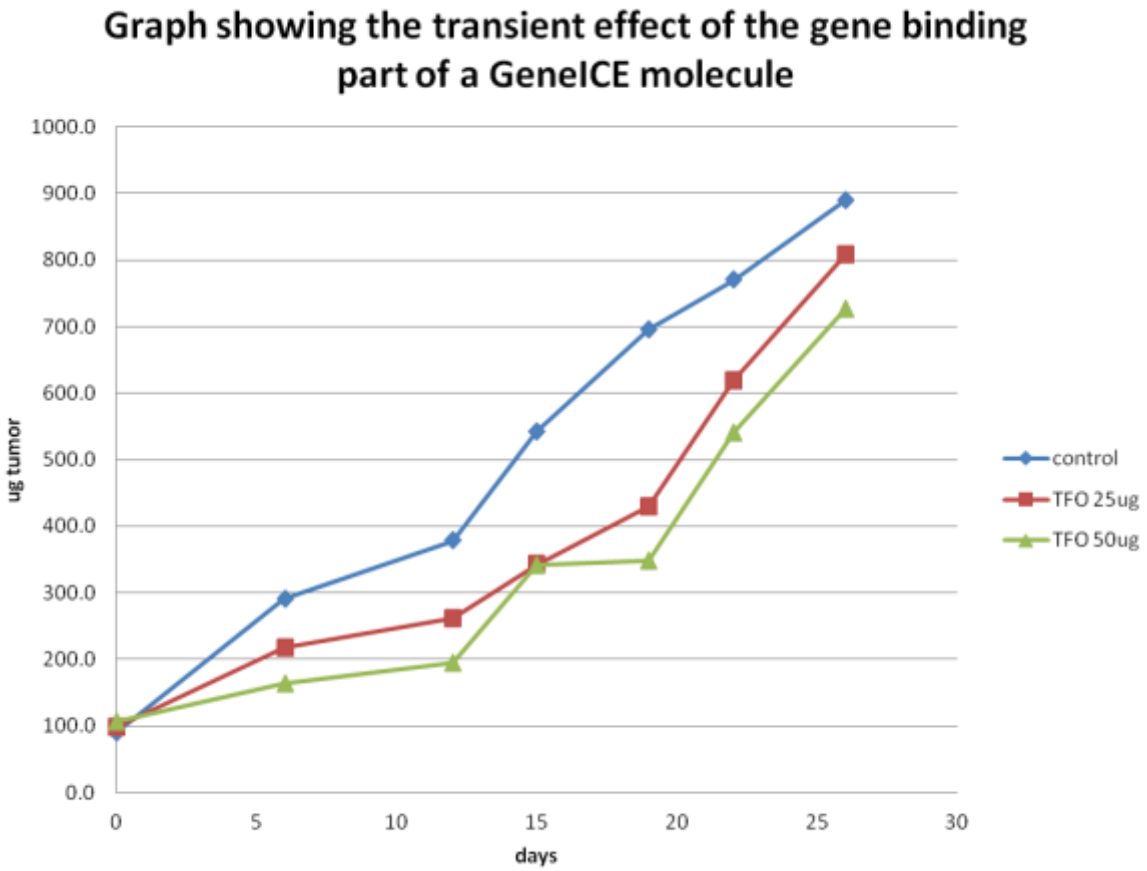
INHIBITION BY GeneICE

GeneICE-POC 1



GeneICE-Transient Effect

GeneICE-POC 2



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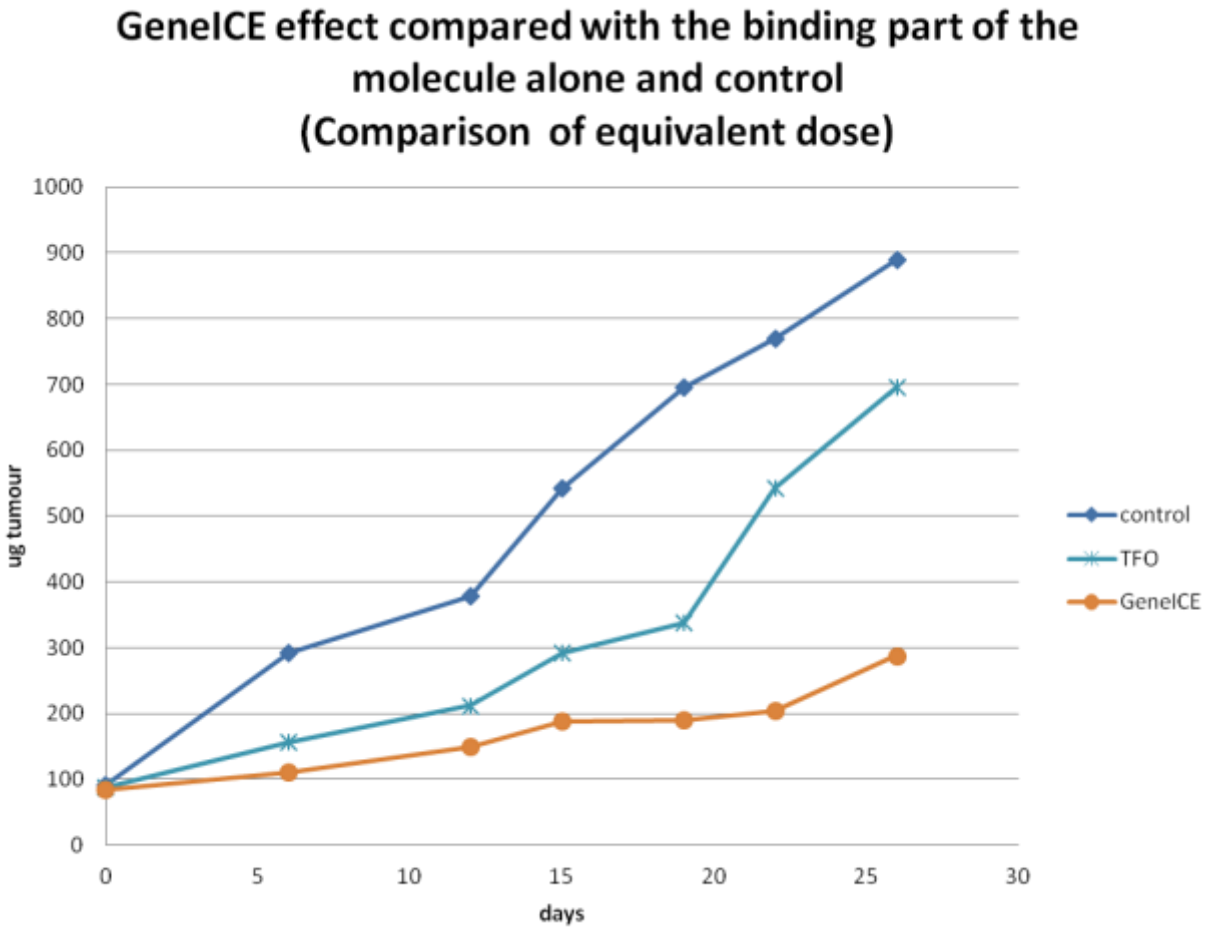
GeneICE Comparison

GeneICE-POC 3



GeneICE IN-VITRO

In-Vitro

Restoration of Apoptosis in LnCAP Prostate Cancer Cells

Control

TFO

50pmol promoter GeneICE

GeneICE & Antisense

Antisense comparison 1

Comparisons with Antisense drugs

The development of antisense drugs has cleared the ground for the development of GeneICE Therapeutics

- ❑ *Acceptability of drugs which act at the level of gene expression*
- ❑ *Establishing a Regulatory framework*
- ❑ *Development of suitable delivery systems*
- ❑ *Stimulated clinical interest in such new therapeutic approaches*

GeneICE & Antisense

Antisense comparison 2

Comparisons with Antisense drugs

Gene ICE Therapeutics	Antisense Drugs
❑ Acts on DNA	❑ Acts on mRNA
❑ Natural silencing	❑ Based on blocking translation
❑ Sustainable silencing	❑ Non-sustainable due to mRNA t/o
❑ High target specificity	❑ Non-specific binding can be a problem
❑ Efficient/reproducible down regulation	❑ Unpredictable/variable down regulation
❑ Low dose, lower toxicity potential	❑ High dose increases toxicity potential

GeneICE SUMMARY

Summary

- ValiRx has developed a proprietary technology for the efficient silencing of genes based on natural mechanisms (GeneICE^{TM})
- ValiRx believes that this technology offers considerable advantages over existing gene validation methods, combining speed, efficiency, selectivity and sustainability as well as its applicability to human cells and *in vivo* determinations
- ValiRx is employing GeneICE to identify new drug targets in hormone regulated cancers (GeneICE Drug Discovery)
- ValiRx is also using GeneICE to develop a new class of therapeutic molecule based on silencing of specific genes at DNA level (GeneICE Therapeutics)