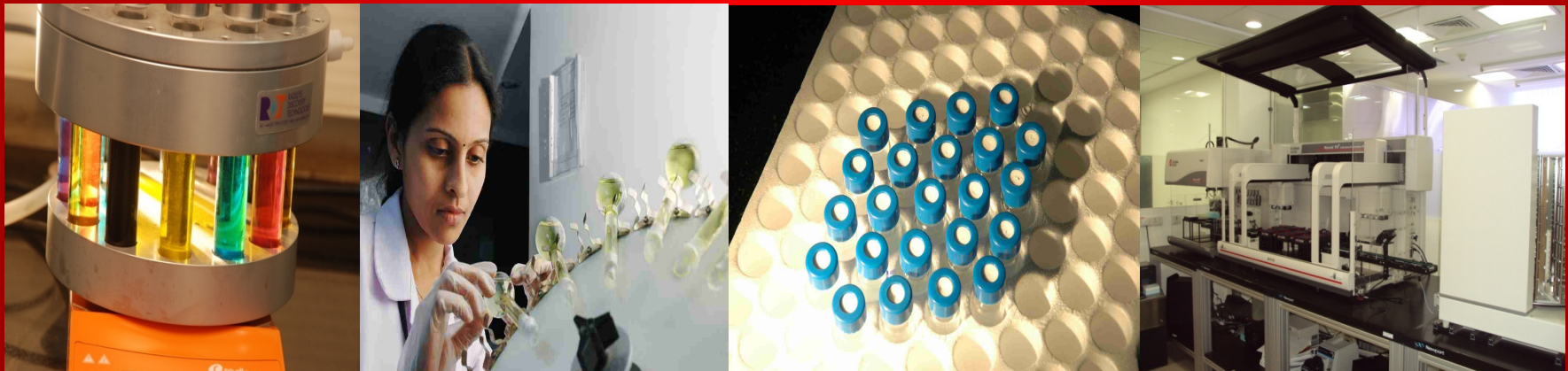


Drug Repurposing & Repositioning Strategies



Outline

- Drug Repurposing - Introduction
- Repurposing Hypothesis
- Repurposing Methods & Positive controls
- Repurposing Process
- Case Studies
- Drug Repurposing Process in detail
- GVKBIO Value Proposition

Drug Re-purposing and/or Re-positioning

- **Drug Re-purposing:** Identification of *additional therapeutics indications for existing marketed drugs or clinical candidates*
- Drug Re-positioning = Drug Re-purposing = Drug Re-profiling = Drug Re-tasking
- The Drug Re-positioning concept evolved in the early 1990s and ~300 FDA approved repurposed drugs are in the market
- It is a strategic approach to drug development **to extract added value from prior Research and Development** investments
- Reinvestigation of drug candidates that have not succeeded in advanced clinical trials **for reasons other than safety** are candidates for potential new therapeutic applications

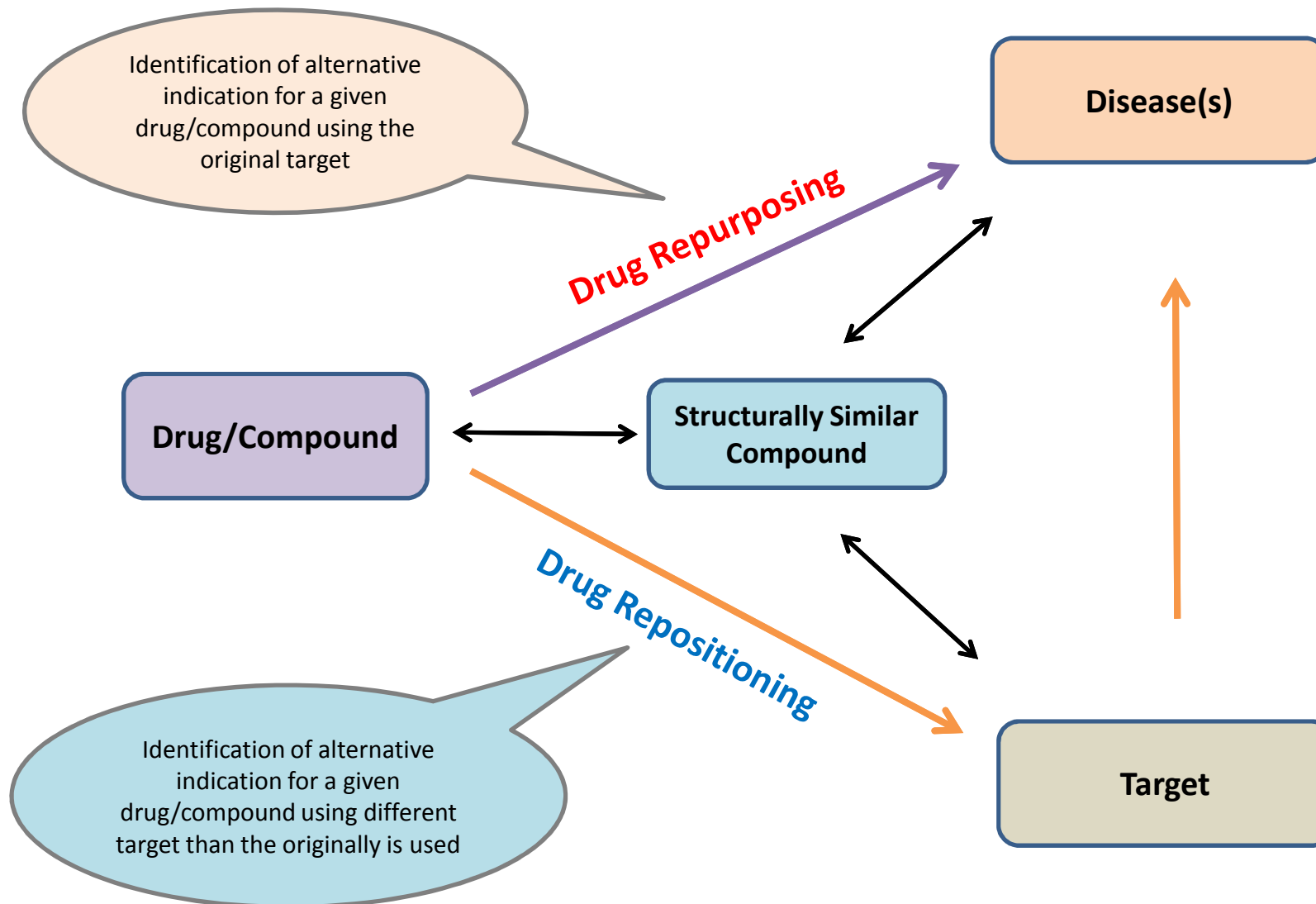


	Drug Development	Drug Repurposing
Cost	\$1B to develop	Fraction of the cost
Time for R&D	12-14 years	2-6 years
Experiments	Complete set	Significantly less
Cost Vs benefit	Lower	Higher
Success rate	Low	Relatively better
Complexity	High	Relatively less

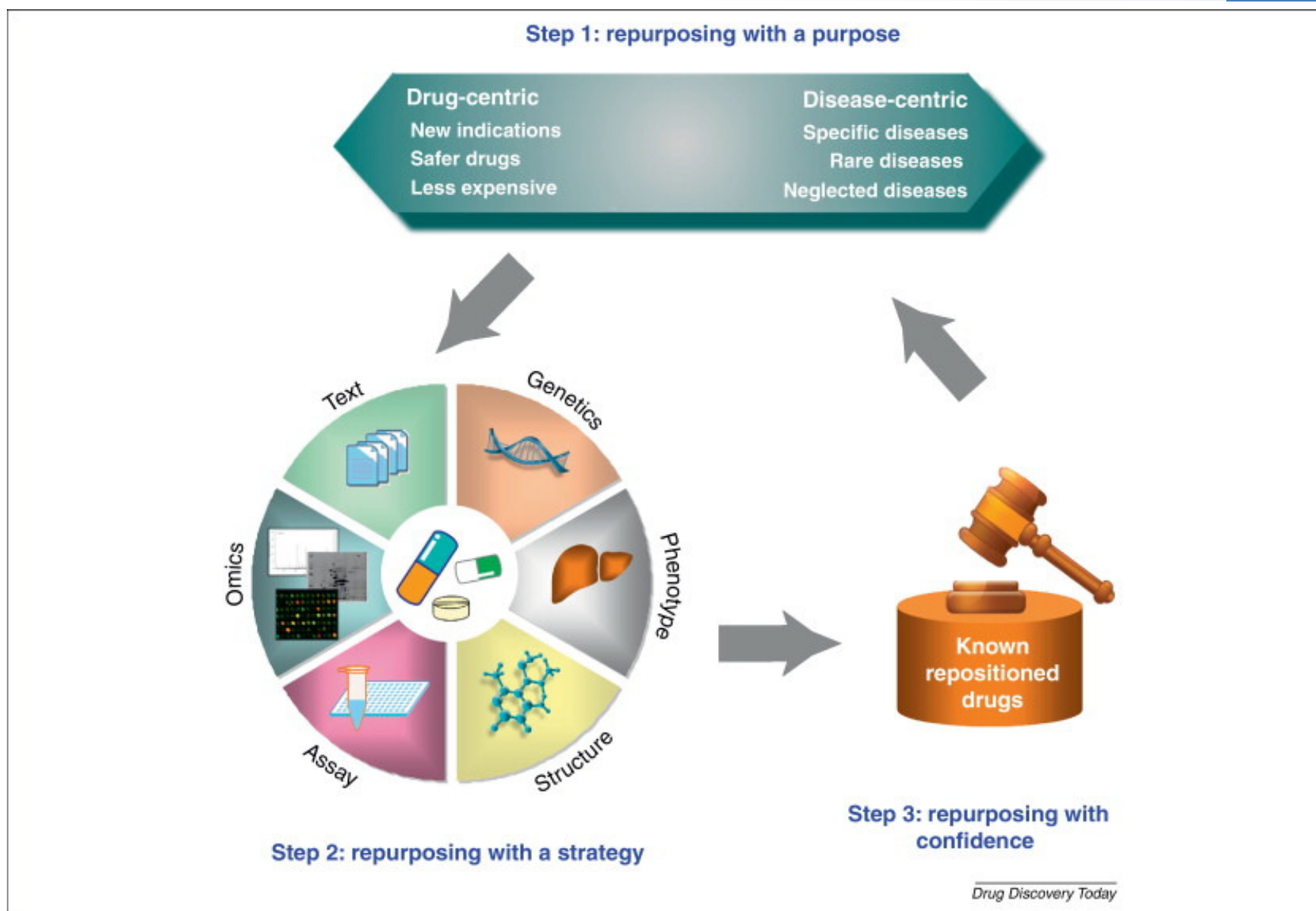
Examples for Repositioned Drugs

DRUG	ORIGINAL INDICATION	NEW INDICATION
Amphotericin B	Fungal Infections	Leishmaniasis
Aspirin	Inflammation, Pain	Antiplatelet
Bromocriptine	Parkinson's Disease	Diabetes mellitus
Finasteride	Prostate hyperplasia	Hair Loss
Gemcitabine	Viral Infection	Cancer
Methotrexate	Cancer	Psoriasis, Rheumatoid arthritis
Minoxidil	Hypertension	Hair Loss
Raloxifene	Cancer	Osteoporosis
Thalidomide	Morning Sickness	Leprosy, multiple myeloma
Sildenafil	Angina	Erectile Dysfunction, pulmonary hypertension

Drug Repurposing & Repositioning

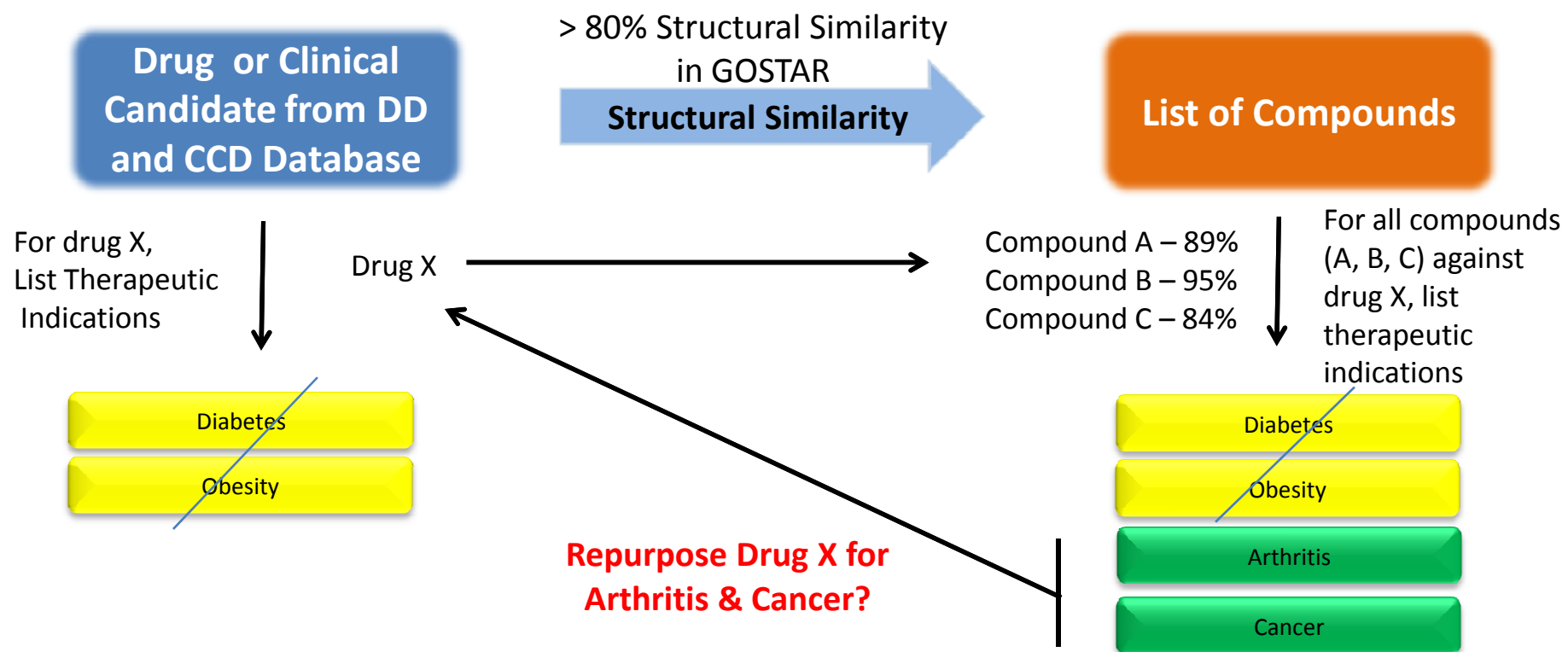


Drug Repositioning Approaches at GVKBIO

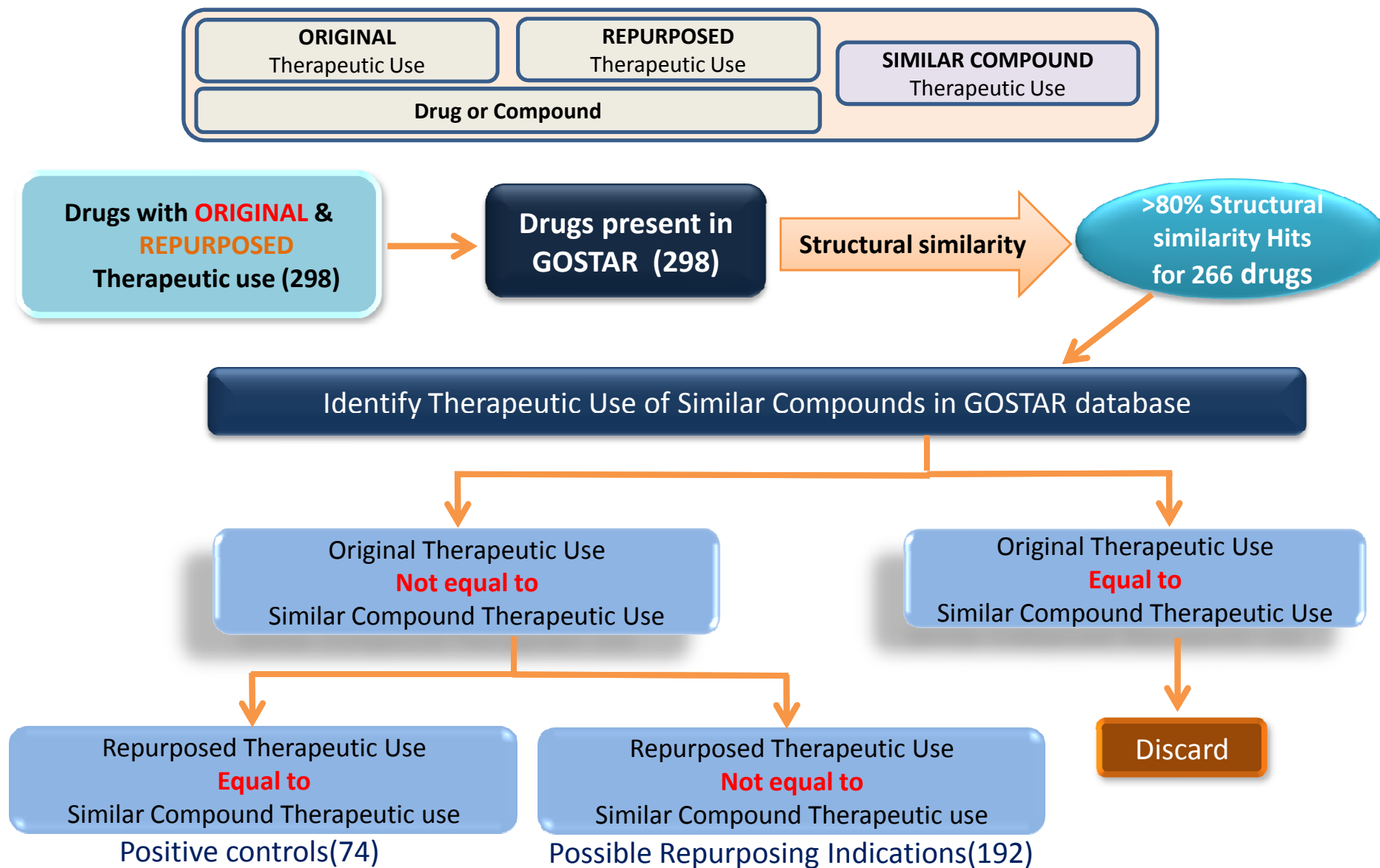


Drug Re-Purposing Hypothesis

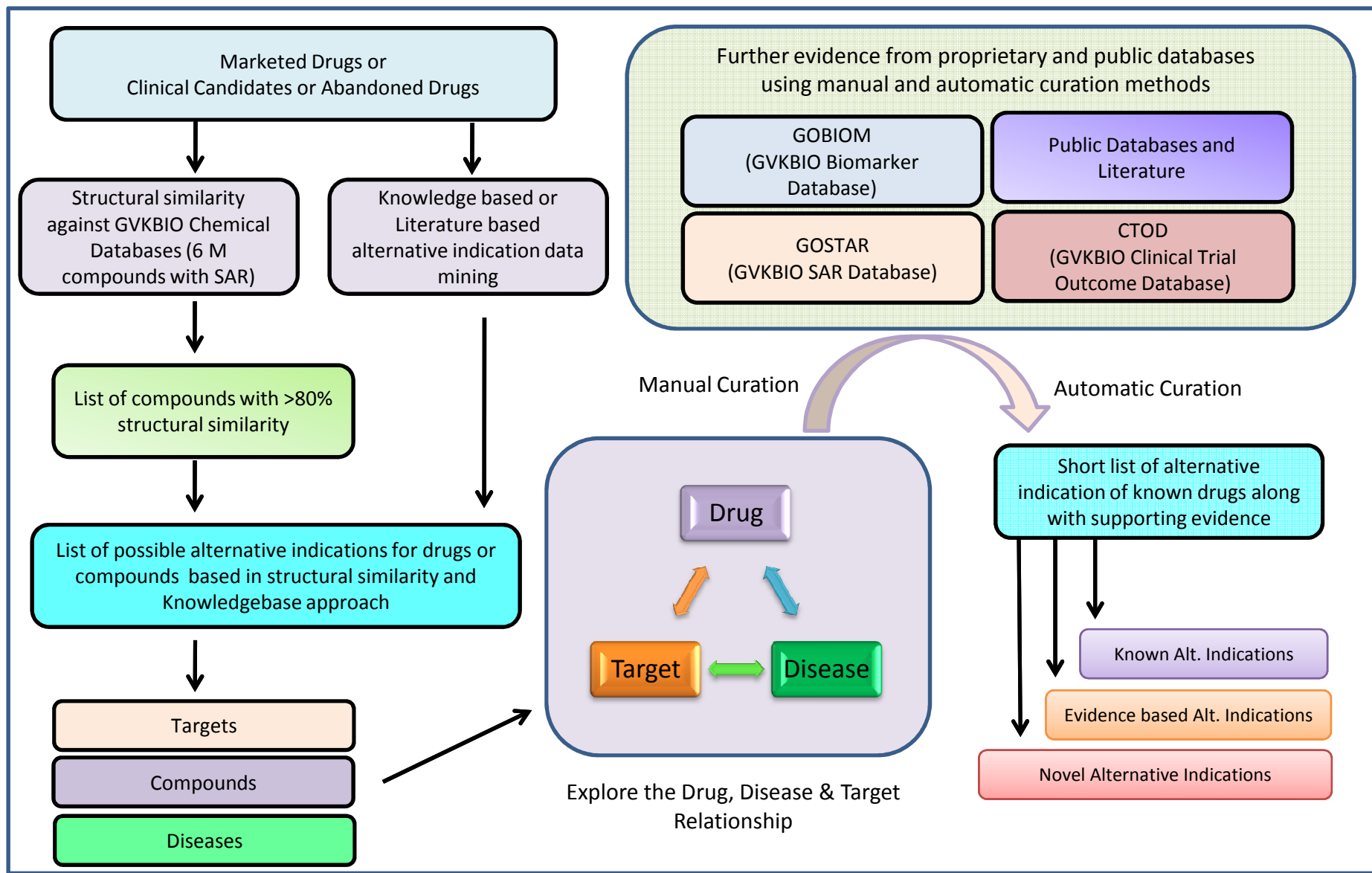
Structural Similarity = Functional Similarity = Possible Alternative Indications



Positive Controls (so called) Work Flow



Drug Repurposing & Repositioning Strategy



Drug Repurposing Case Studies

NIH/NCATS Program for Drug Repurposing

- Discovering New Therapeutic Uses for Existing Molecules Initiative
- Designed to develop partnerships between pharmaceutical companies and the biomedical research community to advance therapeutic development
- NCATS has partnered initially with 8 companies including Pfizer, AstraZeneca, BMS, GSK, Abbott, Janssen, Sanofi and Eli Lilly etc...
- NIH/NCATS Failed Drugs:
 - 58 drugs are listed in NIH/NCATS program
 - Our Drug repurposing algorithm identified possible new therapeutic uses for these failed drugs.

Possible repurposing indications for NIH/NCATS Drugs

DRUG_CODE	ORIGINAL DEVELOPMENT INDICATION(S)	NO.OF OTHER INDICATIONS	NO.OF SIMILAR COMPOUND INDICATIONS	TARGET
AZD0530	Oncology	4	4	c-SRC; ABL
AZD2171	Oncology	1	3	Vascular endothelial growth factor receptor 1,2,3
AZD9056	Chronic obstructive pulmonary disease	4	2	P2X7 Purino receptor
	Crohn's disease			
	Osteoarthritis			
	Rheumatoid arthritis			
ZD4054	Oncology	2	3	endothelin A receptor
	Pulmonary artery hypertension			
ABT-089	Alzheimer's disease	2	8	Nicotinic acetylcholine receptor
	Attention deficit-hyperactivity disorder			
	Schizophrenia			
	Cognitive disorders			
BMS-562086	Major depressive disorder	3	2	Corticotropin-releasing factor 1
	Generalized anxiety disorder			
	Irritable bowel syndrome			
CP-448187	Depression	1		Corticotropin releasing hormone receptor 1
CP-945598	Obesity	1	4	Cannabinoid receptor 1
GW274150	Migraine	5	6	Inducible nitric oxide synthase
	Asthma			
	Rheumatoid arthritis			
	Sepsis			
LY500307	Critical limb ischemia	1	3	Estrogen receptor β
PF-00913086	Endometriosis	4	4	Estrogen receptor 2
PF-03463275	Schizophrenia	1	3	
				Glycine transporter 1
PF-03654746	Narcolepsy	1	1	Histamine H3 receptor
	Cognitive disorder			
	Attention deficit hyperactivity disorder			
	Allergic rhinitis			
PF-04136309	Chronic osteoarthritis pain	1	2	Chemokine C-C motif receptor 2

Possible repurposing indications for NIH/NCATS Drugs

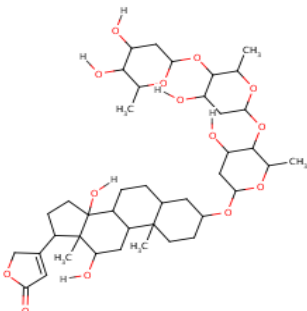
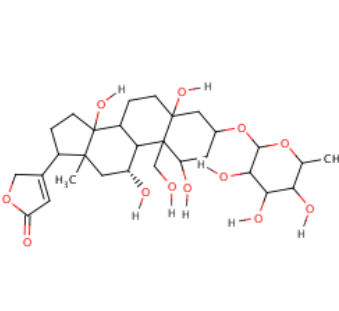
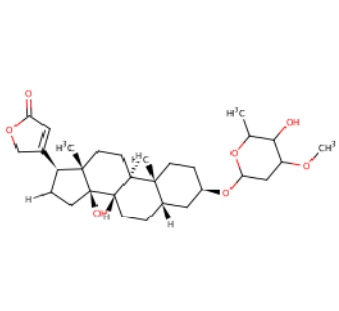
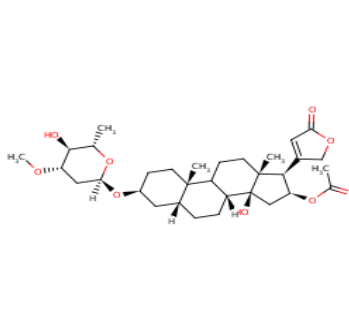
DRUG_CODE	ORIGINAL DEVELOPMENT INDICATION(S)	NO.OF OTHER INDICATIONS	NO.OF SIMILAR COMPOUND INDICATIONS	TARGET
PF-05416266	Sickle cell disease, Asthma	4	6	Potassium intermediate/small conductance calcium-activated channel subfamily N member 4
PH-670187	Generalized anxiety disorder	1	4	5-Hydroxytryptamine 2C receptor;5-Hydroxytryptamine
SB223412	Cough	5	7	Neurokinin receptor 3
	Chronic obstructive pulmonary disease			
	Schizophrenia			
	Irritable bowel syndrome			
	Overactive bladder			
SD-6010	Asthma	2	3	Inducible nitric oxide synthase
	Osteoarthritis pain			
	Disease-modifying osteoarthritis drug			
HMR1766	Angina pectoris	1	3	Guanylate cyclase
	Peripheral artery disease			
	Neuropathic pain			
SAR115740	Acute and chronic pain	2	2	Vanilloid receptor 1
AVE8134	Type II diabetes	3	1	Peroxisome proliferator-activated receptor alpha
SSR149744C	atrial fibrillation	2	3	Amiodarone
AZD5904	Chronic obstructive pulmonary disease	1	10	Myeloperoxidase inhibitor
	Multiple sclerosis			
AZD1981	Asthma	2	10	prostaglandin D2
	Chronic obstructive pulmonary disease			
GSK1004723	Allergic rhinitis	1	6	Histamine H1/H3 receptor
GSK835726	Allergic rhinitis	1	1	Histamine H1/H3 receptor
AZD0328	Cognitive impairment	1	3	Nicotinic acetylcholine receptor alpha 7
PF-05019702	Endometriosis	1	1	Progesterone receptor (PR)
AZD3355	Gastroesophageal reflux disease	1	1	GABA-B receptor
CE-210666	Depression	1	1	5-Hydroxytryptamine 1B receptor
PF-04191834	Asthma	2	1	5-LIPOXYGENASE
AZD1656	Diabetes	2	2	Glucokinase

Digoxin – A Case Study

Drug	Similar Compound Id	Similar Compound Indication	% Similarity
Digoxin	20641930	Cancer	91%
Digoxin	20641928	Cancer	86%
Digoxin	13184022	Ulcer, Leukoderma, Piles, Tumor, Leprosy	90%
Digoxin	13192178	Thrombosis, Tuberculosis, Bacterial Infection, Viral Infection, Cancer	97%
Digoxin	120826634	Inflammatory Diseases, Cancer	97%
Digoxin	13184647	Skin Disease, Cancer	89%
Digoxin	1659834	Alzheimer's Disease	96%

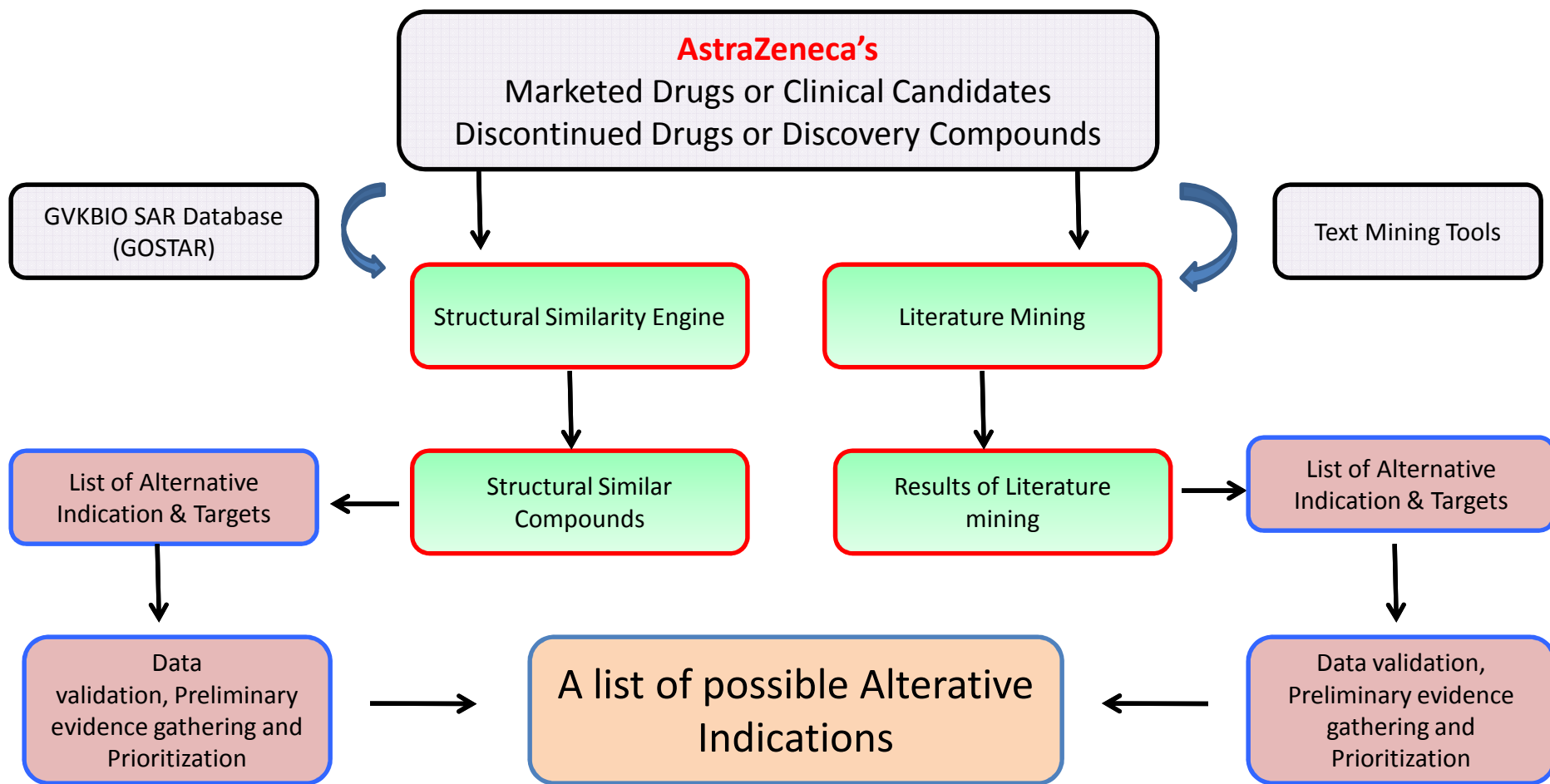
	Drug Primary Information	Drug Repurposing Information
Mechanism of Action	Digoxin blocks sodium-potassium ATPase and increases the amount of calcium and potassium inside heart cells. Its helps the heart contract more forcefully and making it more efficient at pumping blood.	Digoxin inhibits HIF-1a protein synthesis and expression of HIF-1 target genes in cancer cells
Indication	Congestive cardiac insufficiency, arrhythmias and heart failure.	Prostate Cancer ; Breast Cancer; Melanoma
FDA approved disease	Mild-moderate cardiac failure. 1934,	Clinical trial phase II
Company	1934 Glaxowellcome	Thomas Jefferson University, USA

Digoxin and Similar Compounds

	DIGOXIN	SIMILAR COMPOUND 1	SIMILAR COMPOUND 2	SIMILAR COMPOUND 3
STRUCTURE				
% SIMILARITY	---	96.69	97.33	89.57
GVK ID	5900361	1659834	13189027	20635148
COMPOUND NAME	Digoxin	Ouabain	----	Oleandrin
INDICATION	Heart Disease; Arrhythmia	Alzheimer's Disease; Cancer	Arrhythmia; Inflammation; Cardiac Disorder; Cancer	Lung Cancer
MOA& TARGET	Digoxin inhibits the Na-K- ATPase membrane pump, resulting in an increase in intracellular sodium	By inhibiting Prostaglandin-endoperoxide synthase 2	By inhibiting Intercellular adhesion molecule-1	By inhibiting NFKB
CLINICAL TRIALS				Phase 1
SPONSOR				M.D. Anderson Cancer Center

GVKBIO Drug Repurposing Process

Drug Repurposing Process - Phase I

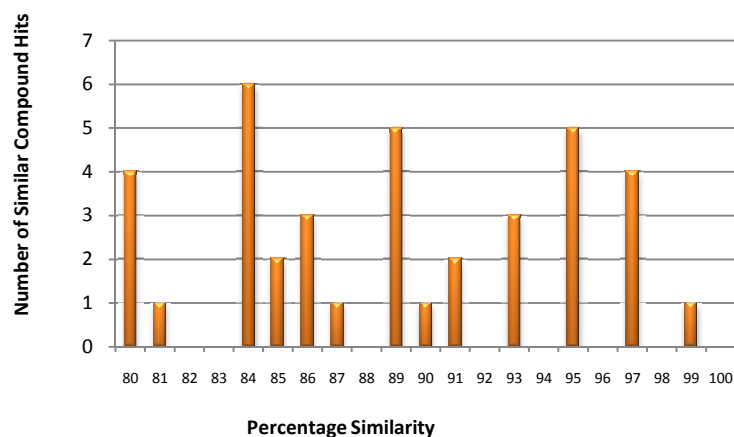


Drug Repurposing Phase 1 Results

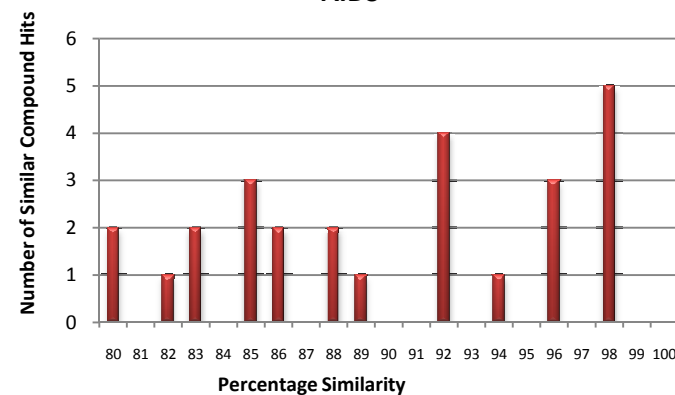
POSSIBLE REPURPOSING INDICATIONS	Priority Score	TARGETS	Priority Score
AIDS	20	Reverse Transcriptase	10
		Integrase	8
Alzheimer's Disease	18	P-glycoprotein	6
		ERK1, ERK2	8
		Protein Kinase C	4
Angiogenesis	6	Tubulin	8
		ERK1, ERK2	8

Possible Repurposing Indications	No. of Hits
DIABETES	38
AIDS	26
RHEUMATOID ARTHRITIS	39
CARDIOVASCULAR DISEASES	38
ALZHEIMER'S DISEASE	28

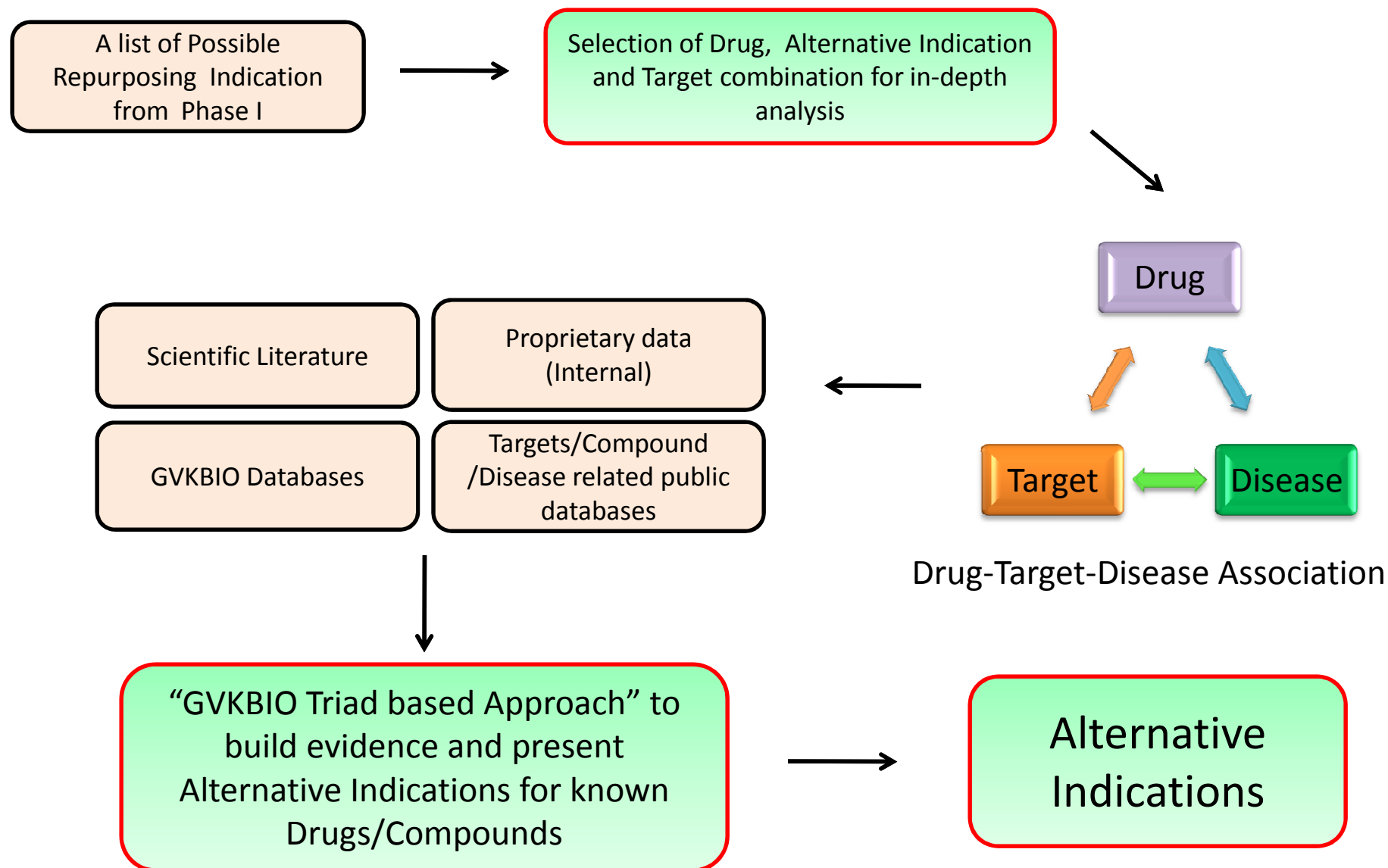
DIABETES



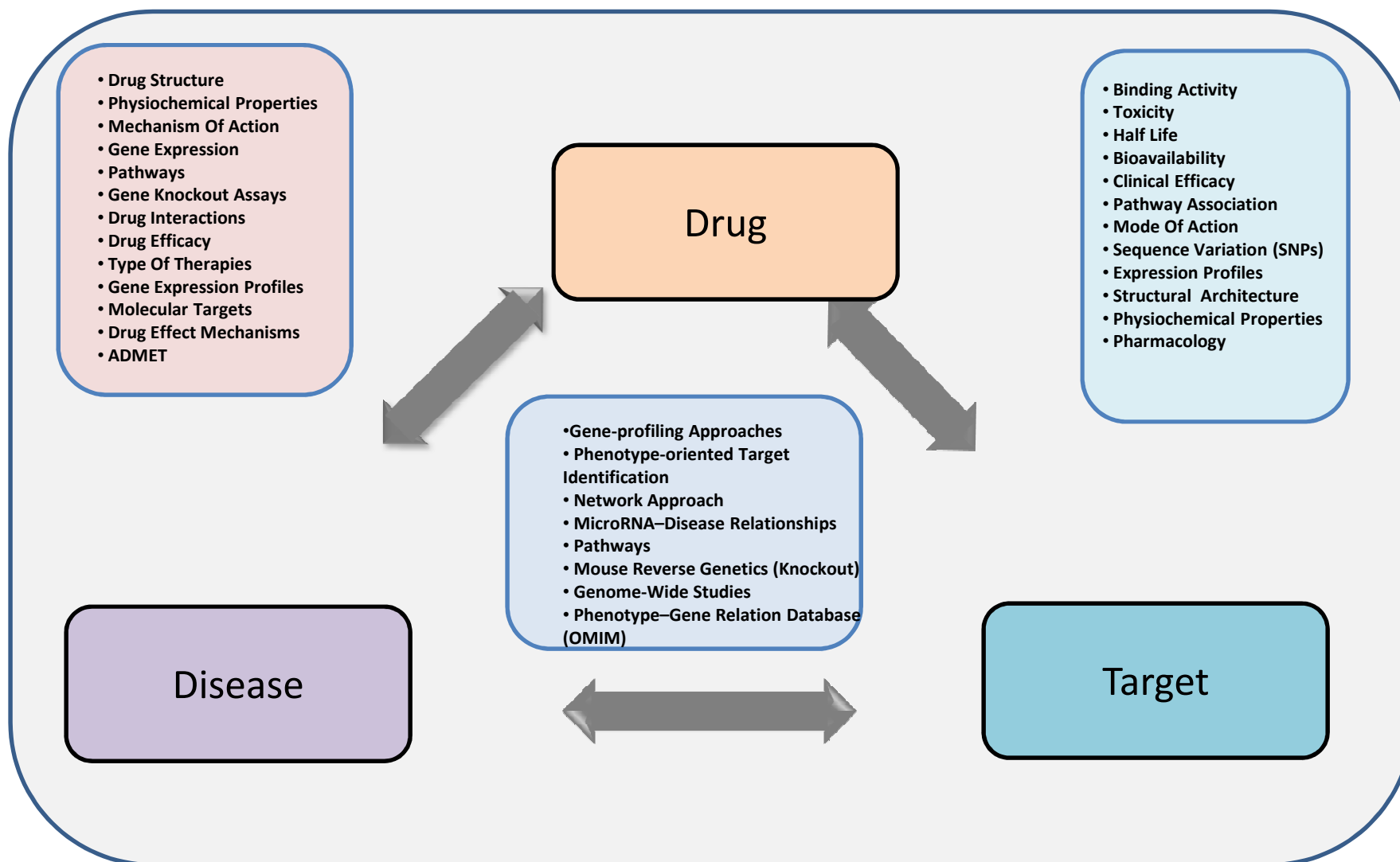
AIDS



Drug Repurposing Process – Phase II



Drug-Disease-Target



Data Analysis and Prioritization

Data analysis and Prioritization may be executed in three different ways:

- Drug Centric Approach
 - Alternative Indication Centric Approach
 - Target Centric Approach
-

Drug Repurposing Analysis Factors

Drug Analysis Factors	Target Analysis Factors	Disease Analysis Factors
Drug Name, Drug Synonyms & Brand Name	Target Name	Disease Names
Molecular Formula & weight	Biochemical Class	Disease Type
Drug Structure	Target Action	Therapeutic Class
Compound Indication	Super family	ICD 10
Mechanism of action	Family	Disease Description
SMILES, Inchi, IUPAC Name and CAS Number	Protein	Disease Category
Pharmacodynamics	Gene Symbol	Disease Pathways
Absorption	Binding Activity	Differentially expressed genes
Volume of Distribution	SNPs	Disease Biomarkers
Metabolism	Functional involvement of Target	List of Pathways contributes the pathology
Drug Route of administration	Pathways related to Target	MicroRNA-Disease Relationships
Drug Route of elimination	Target Expression in different tissues or organs	
Half Life & clearance	Target Over expression phenotypes	
Toxicity & adverse events	Target under expression phenotypes	
Drug Pathway	Genotypic-Phenotypic association of SNPs	
Drug Efficacy	Target interaction with other proteins	
Bioavailability	Target based biomarkers	
Original inventor	miRNAs which regulates the target	
FDA Approved indication and Date	Protein - Protein Interactions	
Current clinical trials		
Drug Drug Interactions		
Pathways perturbed by the drug		
Drug related Biomarker		
Diff Expression after Drug treatment		
GWAS - responder/non-responder information		
Drug association with SNPs		
Binding activity to Target proteins		

GVKBIO Value Proposition

- Hypothesis
- Structure Activity Relationship (SAR) data
- Experience in data curation
- Subject matter expertise
- Multiple business models
 - Drug repurposing Services
 - Drug repurposing Pipeline
- One stop shop to create pre-clinical drug repurposing package



Accelerating Research

 Thank You