DRUG REPOSITIONING FOR DIABETES BASED ON 'OMICS' DATA MINING

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SLIDE SHOW CREATED BY DYLAN LEHRER

DIABETES MELLITUS

- Affects approximately 382 million people worldwide
- Over $548 billion in treatment costs
- Previous diabetes treatments had associated health risks.
- Traditional drug development process is both lengthy (10-17 years) and costly, with a low success rate (< 10%) and a high safety risk.
  - Need for developing diabetic drugs in a more efficient way with reduced safety risks.

DRUG REPOSITIONING

- Reusing marketed (safe/approved) drugs for a new indication/disease.
- Faster – reduces development time (no need for approval)
  - 10 to 17 yrs → 3 to 12 years
- Cheaper – fewer clinical trials and usage of expensive materials
- Safer – toxicity information is more likely to be available.

‘OMICS’ DATA

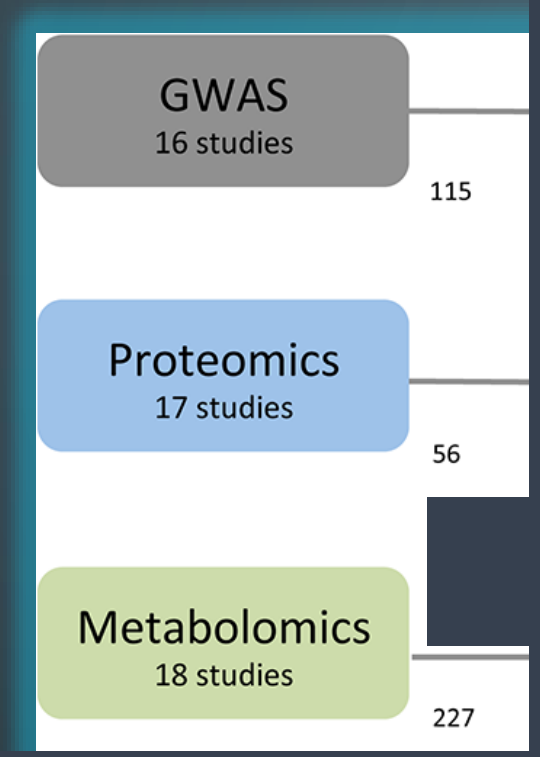
- Experimental data related to diseases
- Technological advancement → more biomedical data available
- **Genomics** - concerned with an organism’s genome, the DNA content that is present within one cell of an organism
  - Genome Wide Association Studies (GWAS) – useful data for drug repositioning
- **Proteomics** - deals with the entire proteome, networks of proteins that can be expressed by organisms
- **Metabolomics** - involves studies of metabolic processes and metabolites, which are low molecular weight biochemicals

MATERIALS AND METHODS

- 1. Literature Search and Data Extraction
- 2. Mining Diabetics Metabolites Related Proteins
- 3. Constructing the Diabetic Metabolites-Proteins Network
- 4. Mapping Diabetes Risk Proteins to Proteins with Drug Projects
- 5. Application of Pathogenesis Information into Anti-Diabetic Drug Repositioning
- 6. Connectivity Map (CMap) Analysis

1. LITERATURE SEARCH AND DATA EXTRACTION

- PubMed database was searched for recent articles that included diabetes and ‘omics’ linked keywords
- Using search results… extracted data from GWAS, proteomics, and metabolomics studies on diabetes.

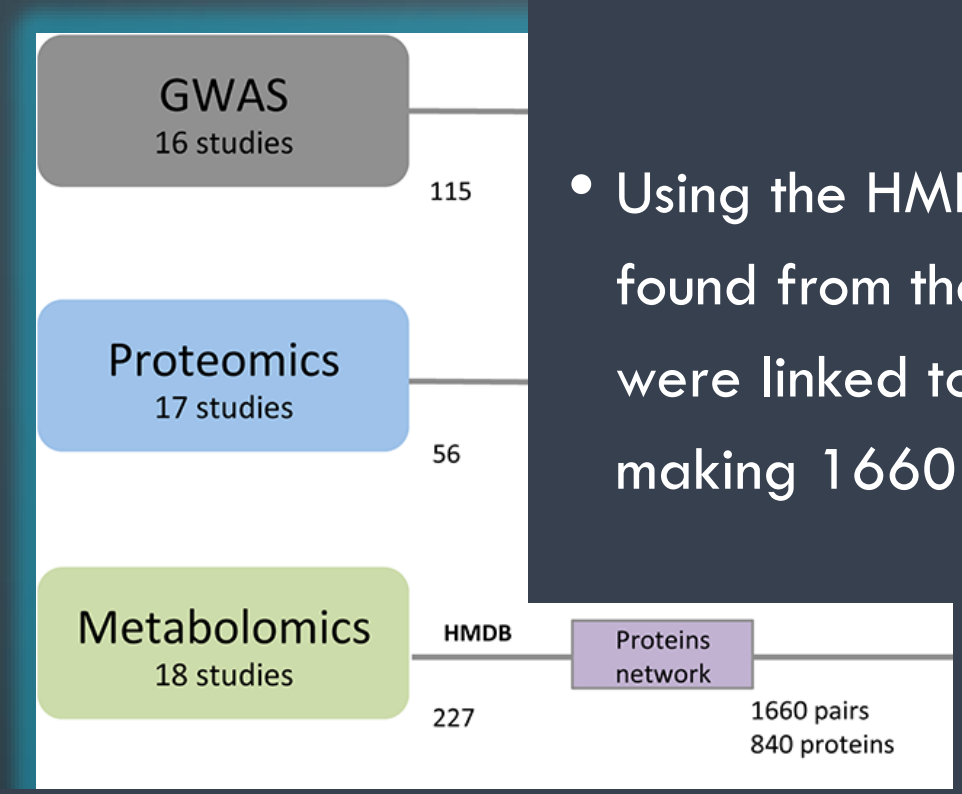


OMICS STUDIES REVEALED DIABETES RELATED GENES, PROTEINS, AND METABOLITES

- PubMed Search – genes, proteins, and metabolites that were reported to be significantly associated with diabetes were selected for further research.
  - 16 GWAS Studies → 115 genes
  - 17 Proteomics Studies → 56 proteins
  - 18 Metabolomics Studies → 227 metabolites

2. MINING DIABETIC METABOLITES RELATED PROTEINS

- Searched the Human Metabolome Database (HMDB) to obtain the names of any proteins (enzymes or transporters) that could be associated with the diabetes related metabolites that were discovered from the previous metabolomics studies found from the literature search.
- Literature Search → Previous Metabolomics Studies
- Previous Metabolomics Studies → Discovered Diabetes Related Metabolites
- Diabetes Related Metabolites → Names of Associated Proteins (Enzymes or Transporters)



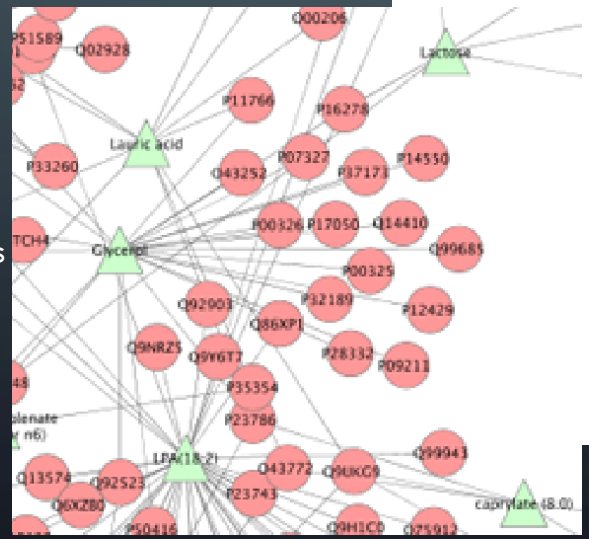
- Using the HMDB, the 227 diabetes associated metabolites found from the metabolomics studies in the literature search were linked to 840 enzymes or transporters (proteins), making 1660 metabolite-protein pairs.

3. CONSTRUCTING THE DIABETIC METABOLITES-PROTEINS NETWORK

- Diabetic Metabolites and their Associated Enzymes/Transporters were visually linked through a metabolites-proteins network.
- Cytoscape (www.cytoscape.org) was used to construct the metabolites-proteins network.

VISUALIZATION OF METABOLITE-PROTEIN NETWORK ASSOCIATED WITH DIABETES

- The metabolite-protein network was generated using Cytoscape.
  - Shows the highly connected metabolic pathways of various metabolites.

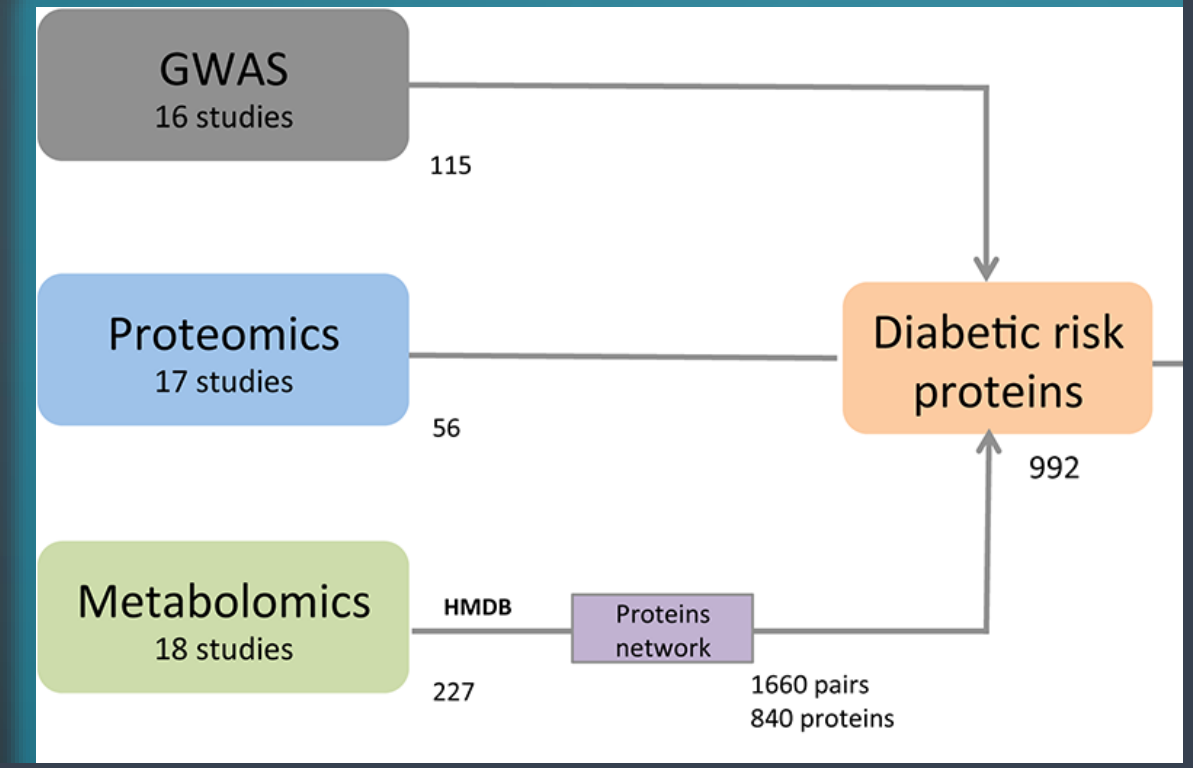


Diabetes Associated Metabolites

Proteins associated with metabolites (based on the HMDB database)

4. MAPPING DIABETES RISK PROTEINS TO PROTEINS WITH DRUG PROJECTS

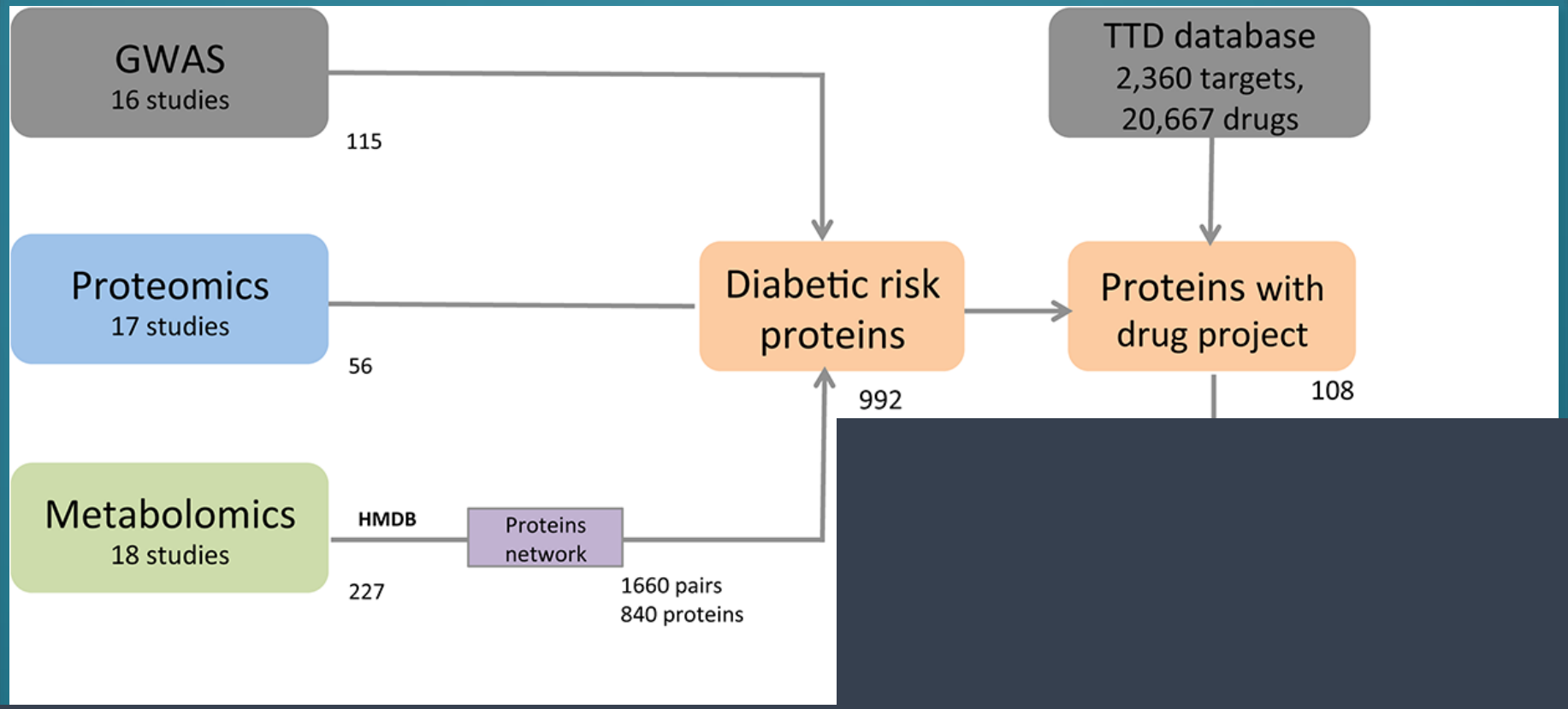
- Literature Search → Genomics and Proteomics Studies → Diabetes Related Genes or Proteins
- Diabetes Related Genes or Proteins + Diabetes Related Proteins from Step 2 → Set of Diabetic Risk Proteins
- Uniprot IDs were retrieved to map the corresponding proteins.



- 840 metabolic proteins associated with diabetic metabolites + 115 genes + 56 proteins → 992 unique diabetic risk proteins.

4. MAPPING DIABETES RISK PROTEINS TO PROTEINS WITH DRUG PROJECTS

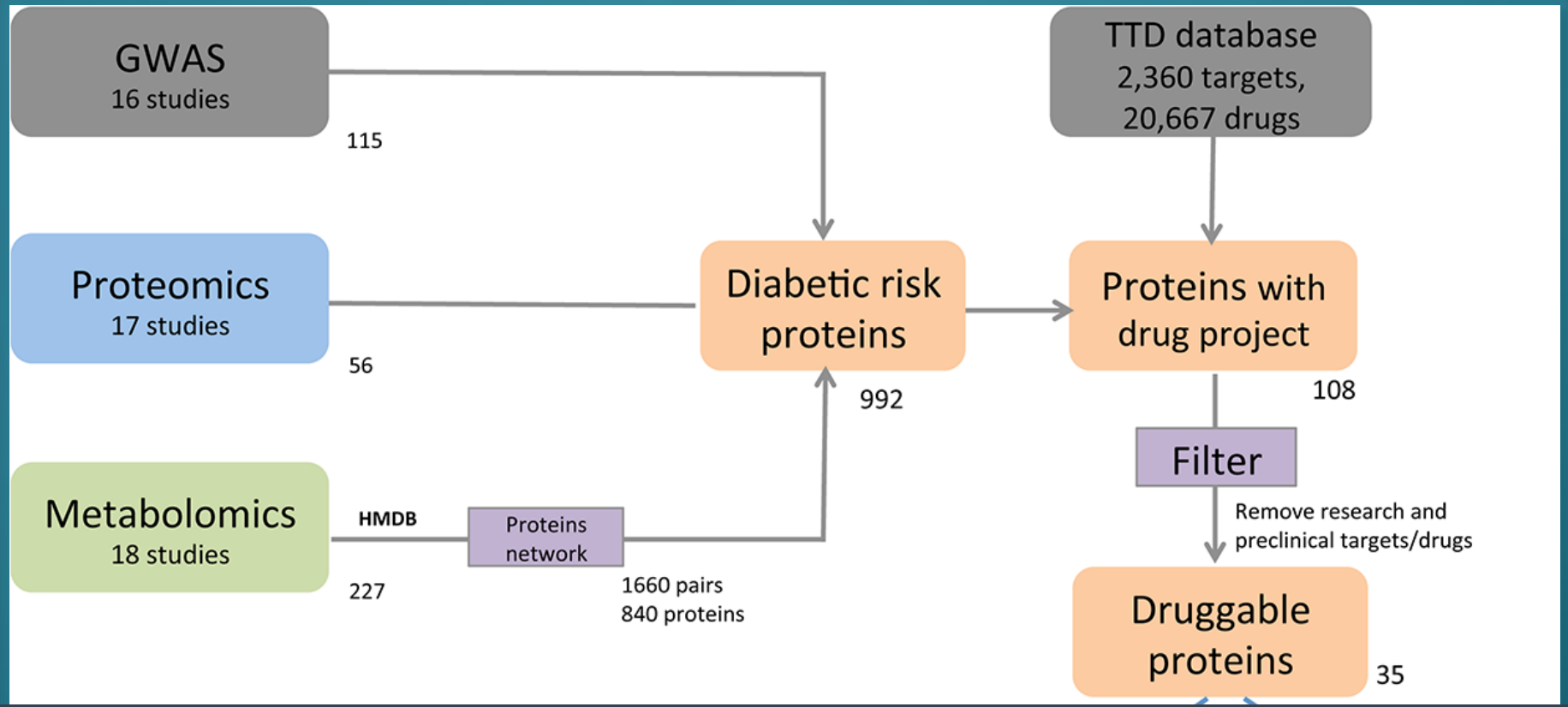
- Therapeutic Target Database (TTD)
  - Contains information on 236 targets of 20,667 drugs at the stages of approved, clinical trial and experimental.
  - Used to find the diabetes risk proteins that had drug projects available.



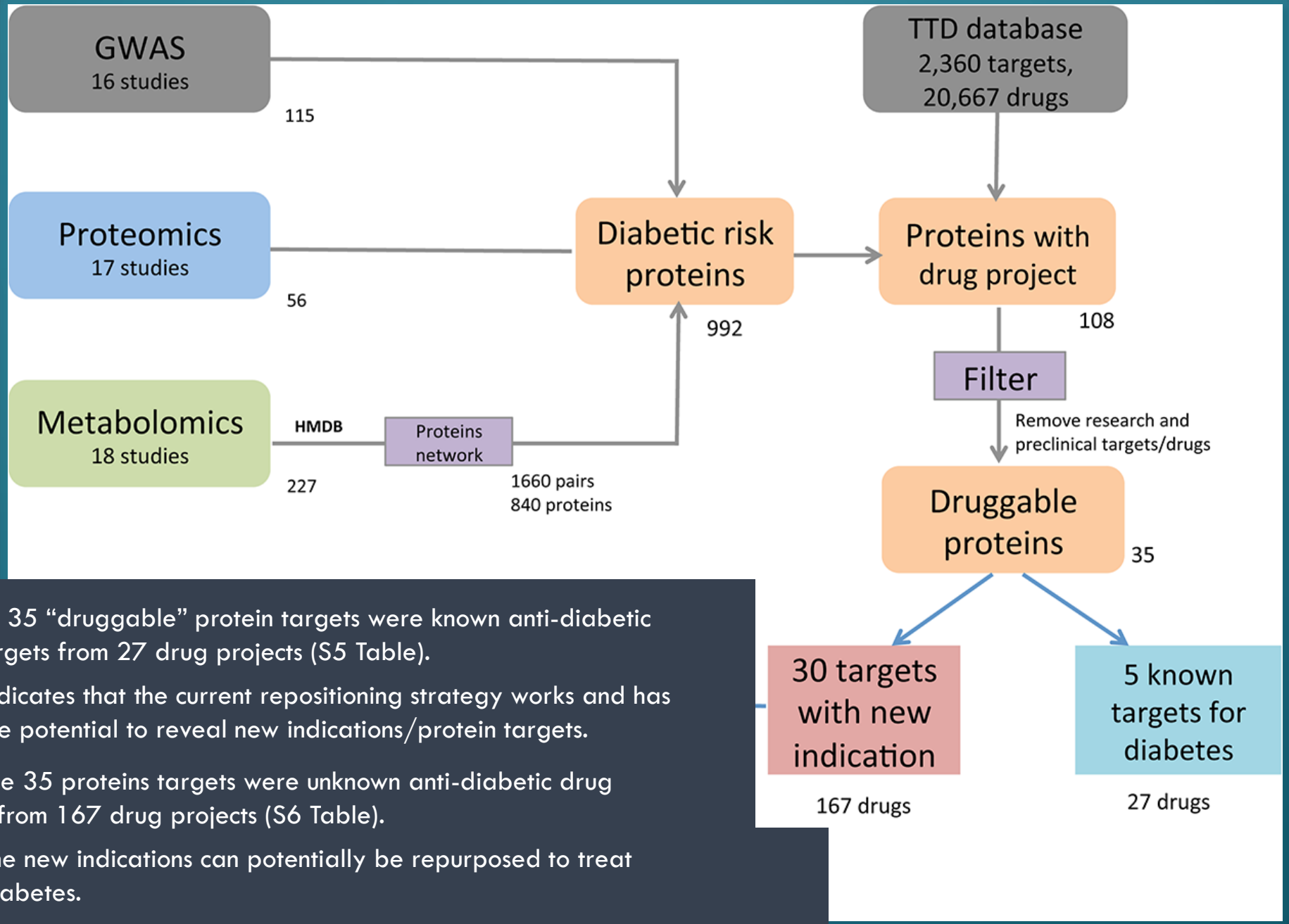
- Using the TTD database, it was found that 108 of the 992 diabetic risk proteins had information on at least one existing drug project.

4. MAPPING DIABETES RISK PROTEINS TO PROTEINS WITH DRUG PROJECTS

- Diabetic risk proteins that had existing drug projects were selected and further filtered.
  - Information on the drug target, current disease indication, drug name, drug development stage, and drug mode of action was collected.
  - Only the targets/drugs at the approved stage or in clinical trials were selected and studied.



- Using the TTD database, it was found that 108 of the 992 diabetic risk proteins had information on at least one existing drug project.
- Drug projects at the research or preclinical stage were filtered out (since they had no toxicity information in humans) to focus on the most promising drug candidates.
  - 35 “druggable” proteins were selected



- 5 of the 35 "druggable" protein targets were known anti-diabetic drug targets from 27 drug projects (S5 Table).
  - Indicates that the current repositioning strategy works and has the potential to reveal new indications/protein targets.
- 30 of the 35 proteins targets were unknown anti-diabetic drug targets from 167 drug projects (S6 Table).
  - The new indications can potentially be repurposed to treat diabetes.

S5 Table. 5 targets and 27 drugs have been used for diabetes treatment or at the stage of clinical trials

Drug name	Current drug indication	Stage	Target	Action mode
Yohimbine	Type2 diabetes, Sexual dysfunction	Phase II	Alpha-2A adrenergic receptor	antagonist
Lisofylline	Type 1 Diabetes	Phase I	Lysophosphatidic acid transferase	inhibitor
AMG 151	Type 2 diabetes	Phase II complete	Glucokinase	activator
AZD1656	Type 2 Diabetes	Phase II	Glucokinase	activator
GK1-399	Type 2 diabetes	Phase I/II	Glucokinase	activator
AZD6370	Type 2 Diabetes	Phase I completed	Glucokinase	activator
AZD5658	Obesity, Diabetes	Phase I	Glucokinase	activator
DS-7309	Diabetes	Phase I	Glucokinase	activator
PSN-101	Diabetes Mellitus Type 1 and 2	Phase I	Glucokinase	activator
TAK-329	Diabetes mellitus	Phase I	Glucokinase	activator
TAK-329	Type 1 diabetes	Phase I	Glucokinase	activator
TTP355	Type 2 diabetes	Phase I	Glucokinase	activator
Pioglitazone	Diabetes mellitus	Approved	PPARG	agonist
Rosiglitazone	Diabetes mellitus	Approved	PPARG	agonist
Troglitazone	Diabetes mellitus	Approved	PPARG	agonist
Rosiglitazone & metformin	Type 2 diabetes	Phase III completed	PPARG	agonist
Rosiglitazone & simvastatin	Type 2 diabetes	Phase III completed	PPARG	agonist
INT131	Type 2 diabetes	Phase II	PPARG	agonist
DB 959	Type 2 diabetes	Phase I	PPARG	agonist
DS-6930	Diabetes	Phase I	PPARG	agonist
DSP-8658	Type 2 diabetes	Phase I	PPARG	agonist

S6 Table. 30 proteins corresponding to 167 drug projects might be repurposed for novel indications for treating diabetes

T2D associated genes/proteins	Disease	Drug name	Type	Target	Action mode
ADRA2A	Attention deficit hyperactivity disorder	Connexyn	Approved	Alpha-2A adrenergic receptor	agonist
	anti-Parkinsonian	Atipamezole	research	Alpha-2A adrenergic receptor	antagonist
	hypertension,hypoplastic left heart syndrome.	Phenoxybenzamine	Aproved	Alpha-2A adrenergic receptor	antagonist
	Major Depressive Disorder	Idazoxan	Phase III withdraw	Alpha-2A adrenergic receptor	antagonist
IGF2BP2	Fibrosis	EXC 001	Phase II	mRNA of IGFBP-8	Antisense
KCNQ1	Hypertension	Indapamide	Approved	Potassium voltage-gated channel subfamily KQT member 1	Blocker
	Multiple Sclerosis	Nerispirdine	Phase II	Potassium voltage-gated channel subfamily KQT member 1	Blocker
PLA2G1B	Inflammation and itching	Clobetasol	Approved	Phospholipase A2	inhibitor
	Inflammatory skin conditions	Clocortolone	Approved	Phospholipase A2	inducer
	Atopic dermatitis	Desonide	Approved	Phospholipase A2	inhibitor
	Inflammatory diseases	Desoximetasone	Approved	Phospholipase A2	inhibitor
	Skin Allergies	Diflorasone	Approved	Phospholipase A2	inhibitor
	Inflammatory diseases	Halobetasol Propionate	Approved	Phospholipase A2	inhibitor
	Inflammatory diseases	Hydrocortamate	Approved	Phospholipase A2	inhibitor
	Inflammatory diseases	Prednicarbate	Approved	Phospholipase A2	inducer
	Giardiasis and cutaneous	Quinacrine	Approved	Phospholipase A2	inhibitor

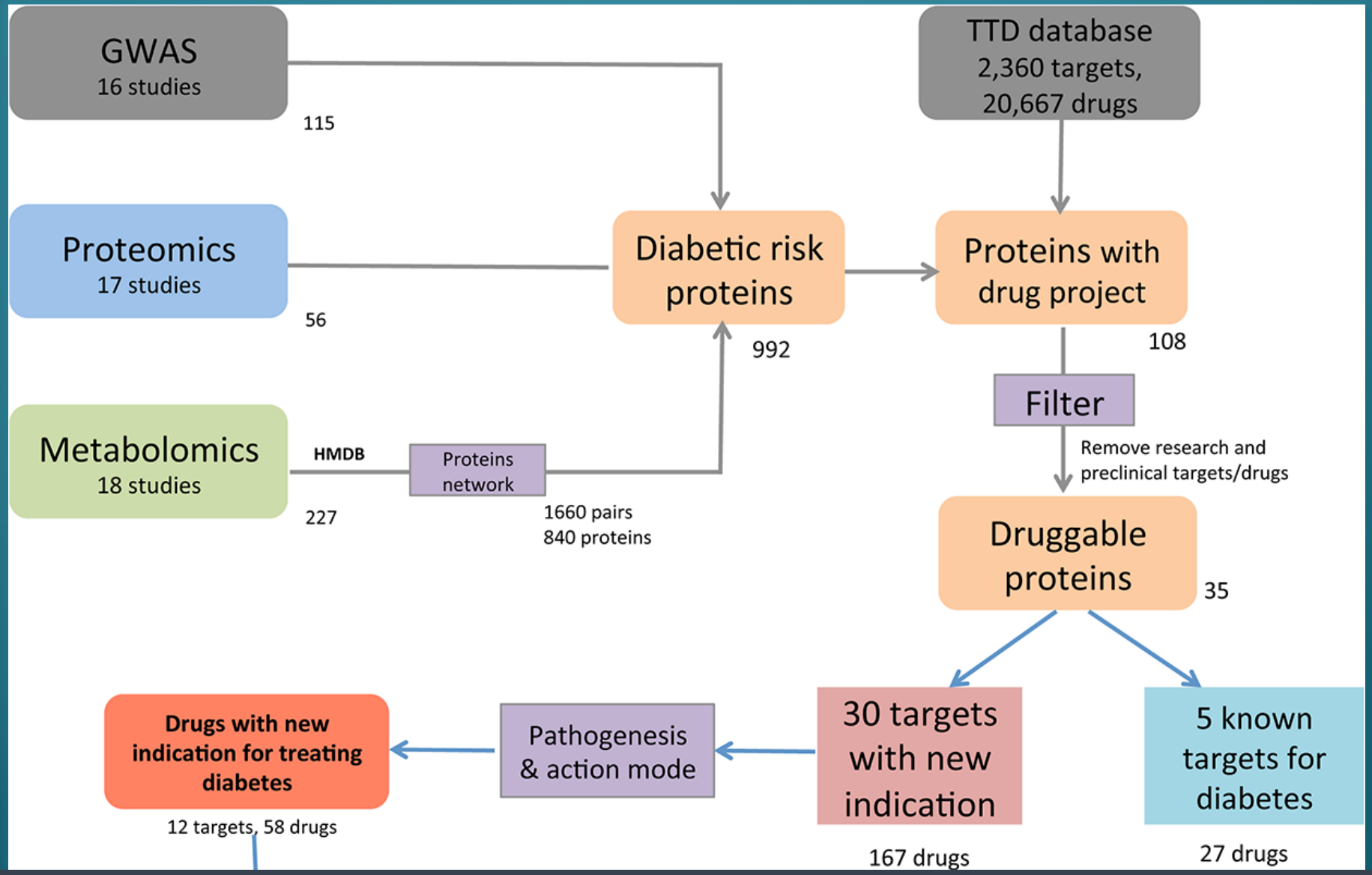
(Full Table Available Online)

5. APPLICATION OF PATHOGENESIS INFORMATION FROM ANTI-DIABETIC DRUG REPOSITIONING

- ‘Omics’ results only suggest associations between proteins and risk of diabetes.
  - Don’t indicate the cause-effect mechanism.
  - Need to understand the pathogenesis (manner of development) of a specific target protein to predict whether the associated drug might improve or worsen the disease phenotype.

5. APPLICATION OF PATHOGENESIS INFORMATION FROM ANTI-DIABETIC DRUG REPOSITIONING

- The Online Mendelian Inheritance in Man (OMIM) database (http://www.omim.org) and a PubMed literature search were used to find information on the pathogenesis (manner of development) of the reduced set of anti-diabetic target proteins.
- Gain of function (GOF) and loss of function (LOF) roles were gathered.
- Drugs that were shown to aggravate diabetic symptoms based on GOF and LOF studies in human/animal models were excluded from further analysis.
  - Ex. If drug D activates target T, and GOF of target T was known to increase diabetes risk, then drug D is more likely to cause diabetes instead of treating it.



- OMIM and a literature search were used to gather GOF and LOF knowledge for the 30 protein targets that had unknown anti-diabetic effects.
- Drug action mode information was gathered from TTD.
- Exclusions: 3 of the 35 targets had no direct pathogenesis link to diabetes, 6 targets were associated with diabetic complications, 14 targets could possibly aggravate diabetic symptoms according to TTD.
- 12 unique protein targets and 58 drugs had pathogenesis information that supported their therapeutic potential for diabetes treatment. One target was already repurposed for diabetes treatment, and one target had a drug project under phase II clinical trial for diabetes treatment.

Information of the 12 targets and 58 drugs repurposed for treating diabetes based on "omics" data mining. (Full Table Available Online)

Drug name	Current drug indication	Stage	Target	Action mode	Pathogenesis
Phenoxybenzamine	Hypertension, hypoplastic left heart syndrome	Approval	Alpha-2A adrenergic receptor	Antagonist	LOF, rescue insulin secretion in congenic islets[#]
Idazoxan	Major Depressive Disorder	Phase III withdraw	Alpha-2A adrenergic receptor	Antagonist	LOF, rescue insulin secretion in congenic islets[#]
Clobetasol	Inflammation and itching	Approved	Phospholipase A2	Inhibitor	GOF, deleterious to normal beta-cell secretory function[15]
Desonide	Atopic dermatitis	Approved	Phospholipase A2	Inhibitor	GOF, deleterious to normal beta-cell secretory function[15]
Desoximetasone	Inflammatory diseases	Approved	Phospholipase A2	Inhibitor	GOF, deleterious to normal beta-cell secretory function[15]
Diflorasone	Skin Allergies	Approved	Phospholipase A2	Inhibitor	GOF, deleterious to normal beta-cell secretory function[15]
Halobetasol Propionate	Inflammatory diseases	Approved	Phospholipase A2	Inhibitor	GOF, deleterious to normal beta-cell secretory function[15]
Hydrocortamate	Inflammatory diseases	Approved	Phospholipase A2	Inhibitor	GOF, deleterious to normal beta-cell secretory function[15]
Quinacrine	Giardiasis and cutaneous leishmaniasis	Approved	Phospholipase A2	Inhibitor	GOF, deleterious to normal beta-cell secretory function[15]
Miltefosine	Visceral Leishmaniasis, Fungal diseases	Phase II	Phospholipase A2	Inhibitor	GOF, deleterious to normal beta-cell secretory function[15]
Varespladib	Coronary Artery Disease, Atherosclerosis	Phase II	Phospholipase A2	Inhibitor	GOF, deleterious to normal beta-cell secretory function[15]
Echothiophate Iodide	Chronic glaucoma	Approved	Cholinesterase	Inhibitor	LOF, potentiate insulin action[16]
Hexafluronium bromide	Spasms, Pain	Approved	Cholinesterase	Inhibitor	LOF, potentiate insulin action[16]
Hydrocortisone	Inflammatory diseases	Approved	Nitric oxide synthase, inducible	Inhibitor	GOF, impair beta-cell function[#]; LOF, reversed fasting hyperglycemia[17]
Carprofen	Pain	Approved	Prostaglandin G/H synthase 2	Inhibitor	LOF, increase insulin secretion[18]; GOF, IDDM[19]
Celecoxib	Rheumatoid arthritis and osteoarthritis	Approved	Prostaglandin G/H synthase 2	Inhibitor	LOF, increase insulin secretion[18]; GOF, IDDM[19]

6. CONNECTIVITY MAP (CMAP) ANALYSIS

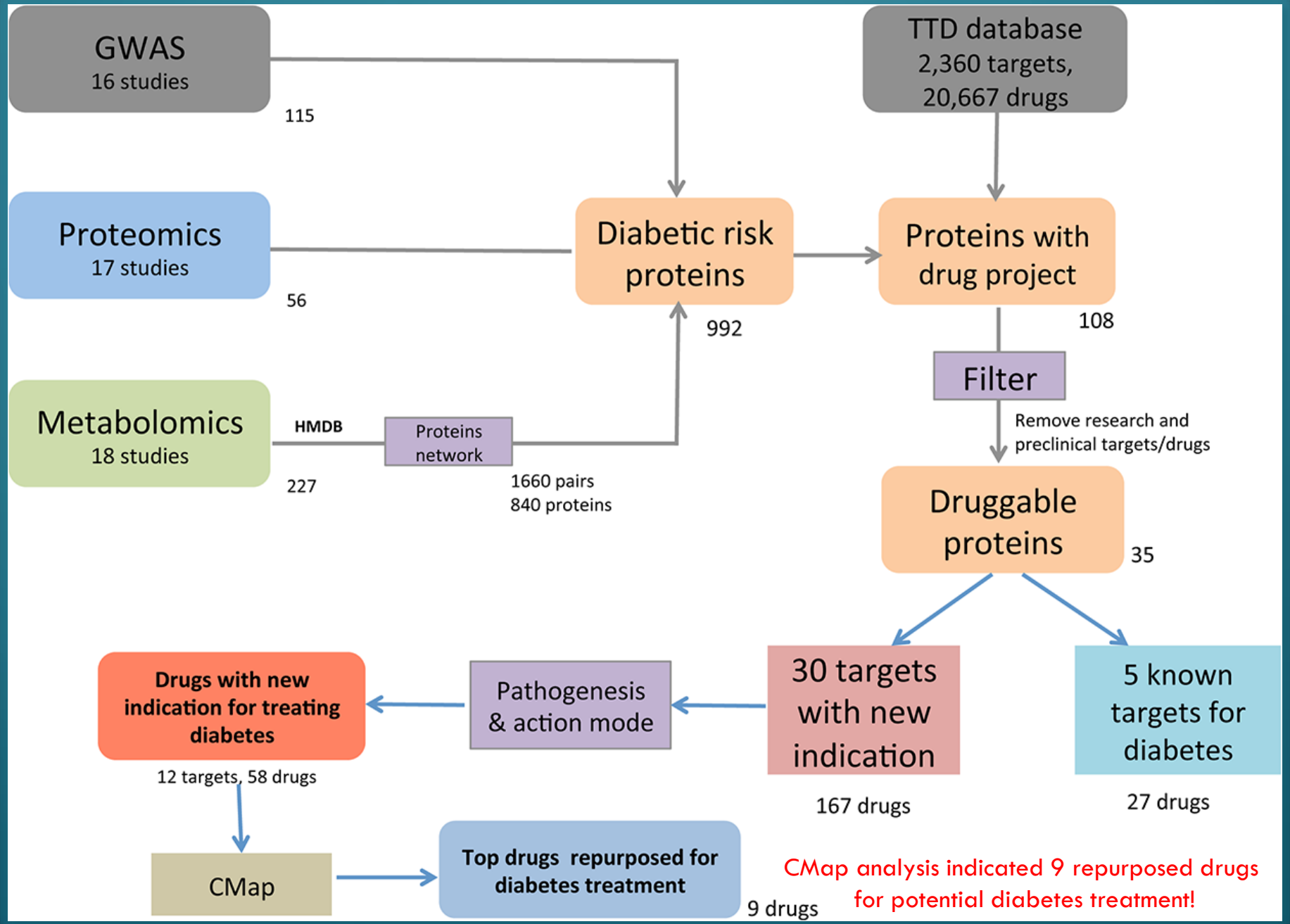
- CMap – a collection of genome-wide transcriptional expression data from cultured human cells treated with compounds, and simple pattern-matching algorithms.
- Candidate drugs gathered from the previously outlined analysis were input into CMap.
  - Evaluated whether they were positively associated with known anti-diabetic drugs or acted in an aggravating manner with known diabetes risk compounds from existing studies.

CONNECTIVITY MAP (CMAP) ANALYSIS

- The 58 drugs with novel indications for treating diabetes were analyzed by CMap.
- 9 of 58 drugs had CMap Information relating to anti-diabetic drugs or diabetic risk compounds.
- 11 of 58 drugs had CMap data, but didn't have links to anti-diabetic drugs or diabetic risk compounds.
- 38 of 58 drugs had no CMap data.

S7 Table. CMap analysis of 58 drugs. (Full Table Available Online)

Drug name	Drug target	Omics method	Current drug indication	cmAP	P-Value
Phenoxybenzamine	Alpha-2A adrenergic receptor	GWAS	hypertension, hypoplastic left heart syndrome	resveratrol (0.799)	0.034
Idazoxan	Alpha-2A adrenergic receptor	GWAS	Major Depressive Disorder	gliclazide (0.728)	0.011
Clobetasol	Phospholipase A2	Metabolomics	Inflammation and itching	ns	
Desonide	Phospholipase A2	Metabolomics	Atopic dermatitis	na	
Desoximetasone	Phospholipase A2	Metabolomics	Inflammatory diseases	na	
Diflorasone	Phospholipase A2	Metabolomics	Skin Allergies	streptozocin (-0.709)	0.015
Halobetasol Propionate	Phospholipase A2	Metabolomics	Inflammatory diseases	na	
Hydrocortamate	Phospholipase A2	Metabolomics	Inflammatory diseases	na	
Quinacrine	Phospholipase A2	Metabolomics	Giardiasis and cutaneous leishmaniasis	na	
Miltefosine	Phospholipase A2	Metabolomics	Visceral Leishmaniasis, Fungal diseases	na	
Varespladib	Phospholipase A2	Metabolomics	Coronary Artery Disease, Atherosclerosis	na	
Echothiophate Iodide	Cholinesterase	Metabolomics	Chronic glaucoma	na	
Hexafluronium bromide	Cholinesterase	Metabolomics	Spasms, Pain	na	
Hydrocortisone	Nitric oxide synthase, inducible	Metabolomics	Inflammatory diseases	na	
carprofen	Prostaglandin G/H synthase 2	Metabolomics	Pain	na	


GWAS
16 studies
115
TTD database
2,360 targets,
20,667 drugs
Proteomics
17 studies
56
Diabetic risk proteins
992
Proteins with drug project
108
Filter
Remove research and preclinical targets/drugs
Metabolomics
18 studies
HMDB
227
Proteins network
1660 pairs
840 proteins
Druggable proteins
35
30 targets with new indication
167 drugs
5 known targets for diabetes
27 drugs
Pathogenesis & action mode
Drugs with new indication for treating diabetes
12 targets, 58 drugs
CMap
Top drugs repurposed for diabetes treatment
9 drugs
CMap analysis indicated 9 repurposed drugs for potential diabetes treatment!

NOTES

- The Therapeutic Target Database (TTD) was used to map diabetes risk proteins to drug projects in this study, but other databases such as DrugBank (http://www.drugbank.ca) may also be useful in finding additional information for disease related proteins and to validate initial findings.