Seeking a novel foundation for a repurposing strategy to treat ultra-rare diseases

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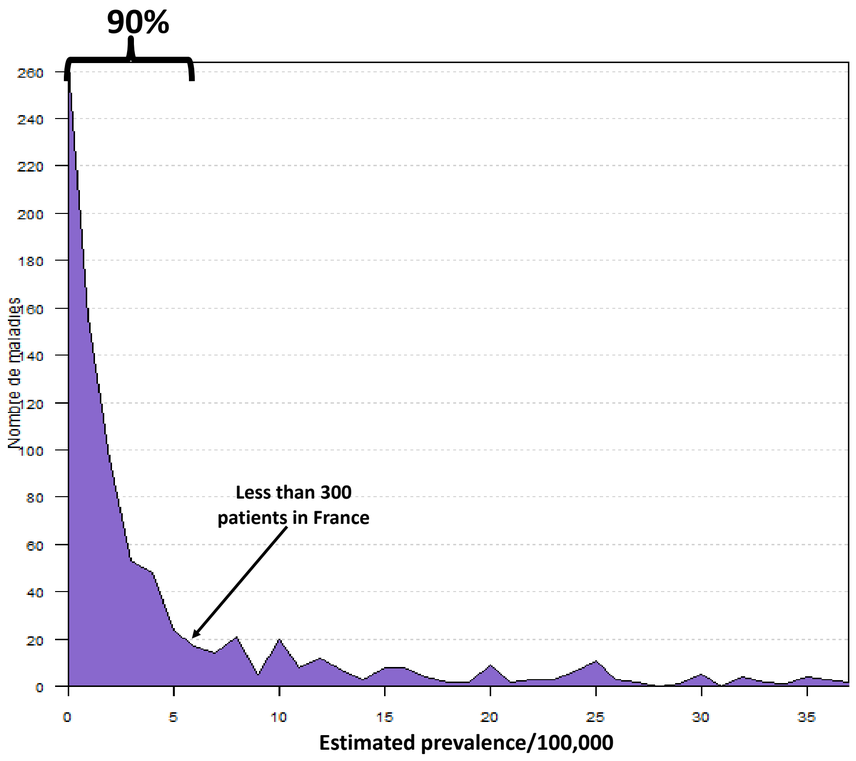
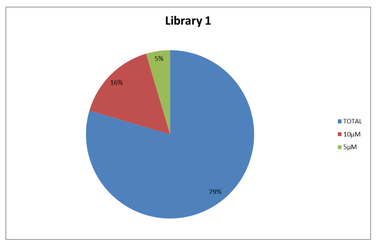


INTRODUCTION

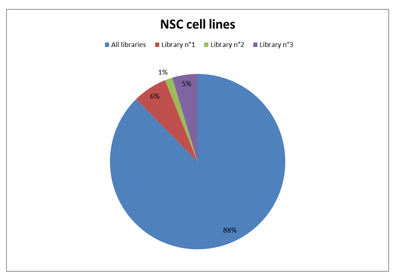
Amongst the 7000+ diseases classified as rare (<5/10,000), the vast majority -probably over 90%- concern less than 30,000 patients worldwide and may be referred to as “ultra-rare”. This is not an official classification but it reveals, nevertheless, that most of those are outside the scope of the pharma industry since, within reasonable pricing, there is no hope of a financial return matching the R&D investment. This, is the more frustrating that recent breakthroughs in terms of cell (e.g., iPS) and molecular biology (e.g., CRISPR/Cas9) now make it feasible to generate and analyze in laboratories experimental models of any genetic disease, whatever the number of affected patients. This may open the path for large-scale in vitro drug discovery process, provide costs of secondary development of the identified hit compounds be reduced to a minimum.
This is the objective of our research project that aims at creating a customizable chemical library of clinically-relevant drugs (e.g., FDA-approved), each of them being tested in cells at the most effective concentrations establishes by the scientific literature.

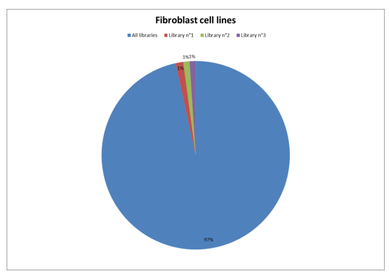
1. I-STEM EXPERIENCE

- **Too many compounds are toxic in a classic doses range**



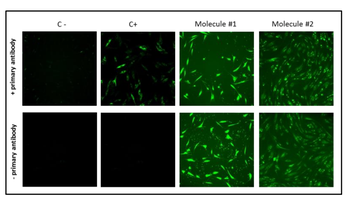
- **Compound toxicity also depends on cellular models**





- **Take into account false positive with technic origin**

HCS Read-out : autofluorescence molecules



HTS Read-out :
- ATP like with Viability test like CTG
- TruHits for AlphaScreen technology
- …

- **Solubility problems may occurred at conventional storage doses**

2. STARTING POINT IN THE FDA LISTING OF COMPOUNDS

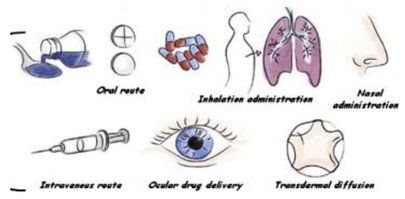
- **Identify clinically-irrelevant compounds**
  - contrast agents for radiology
  - compounds for cosmetics
  - herbicides
  - Veterinary-only compounds

- **Identify toxic compounds in our cellular models**

PD173952	Bay 11-7082	Diphenyleneiodonium chloride	PD-161570	Emetine dihydrochloride hydrate	Idarubicin
BBMP	2-methoxyestradiol	Dequalinium chloride hydrate	N-Oleoyldopamine	Colchicine	AC-93253 iodide
Caffeic acid phenethyl ester	Gemcitabine hydrochloride	Terfenadine	Ouabain	Brefeldin A from Penicillium bref	Auranofin
SKF 96365	PD-407824	CHM-1 hydrate	beta-Lapachone	Chelerythrine chloride	Amsacrine hydrochloride
Bay 11-7085	(S)-(+)-Camptothecin	Iodoacetamide	PD-166285 hydrate	Cyclosporin A	Cantharidic Acid
Rotenone	Topotecan hydrochloride hydrate	Etoposide	Pyrocatechol	CGP-74514A hydrochloride	Quinacrine dihydrochloride
IC 261	Tyrphostin A9	Rottlerin	Vincristine sulfate	Ivermectin	Calcimycin
Cytosine-1-beta-D-arabinofuranoside	Sanguinarine chloride	BIX 01294 trihydrochloride hydra	NNC 55-0396	Cantharidin	…
Stattic	Vinblastine sulfate salt	Nocodazole	Mitoxantrone	Retinoic acid p-hydroxyanilide	
Dihydroouabain	Thapsigargin	Podophyllotoxin	Bromoacetyl alprenolol mer	BIO	

- **Identify median-concentration efficiency**

- **Identify route of administration**



- **Identify cellular models tested**

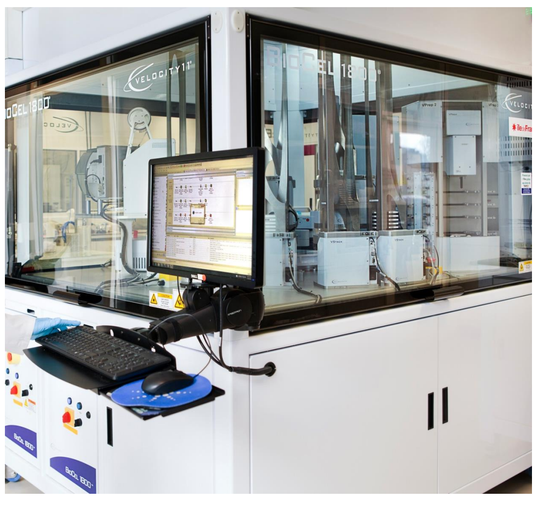
1. FIRST RESULTS

NAME	STRUCTURE	Indication FDA / méca connu	DMSO Solubility mM	CAS No	STORAGE
Fludrocortisone acetate		Anti inflammatoire (mineralocorticoide) glucocorticoid-receptor agonist	198.82 mM	514-36-3	3 years -20°C powder 2 years -80°C in solvent
Fluoxetine		Antidepresseur selective serotonin-reuptake inhibitor	199.54 mM	56296-78-7	3 years -20°C powder 2 years -80°C in solvent
Indacaterol		Asthme + BPCO-adrenoceptor agonist	132.48 mM	312753-06-3	3 years -20°C powder 2 years -80°C in solvent
Salbutamol		Asthme + bronchite + amphyseme -adrenoceptor agonist	196.39 mM	18559-94-9	3 years -20°C powder 2 years -80°C in solvent
Spironolactone		antagonist of the androgen receptor (acne, hirsutism and androgenic alopecia)	199.24 mM	52-01-7	3 years -20°C powder 2 years -80°C in solvent
Fenofibrate		antilipemic reduces cholesterol + TG in the blood PPARalpha activator peroxisome proliferator	199.53 mM	49562-28-9	3 years -20°C powder 2 years -80°C in solvent
Fluconazole		Antinfongique (thiazole) lanosterol 14 alpha-demethylase inhibitor	199.17 mM	86386-73-4	3 years -20°C powder 2 years -80°C in solvent
Furosemide		diurétique	199.55 mM	54-31-9	3 years -20°C powder 2 years -80°C in solvent
Gliclazide		Antidiabétique type II (sulfonylurées) ATP-sensitive potassium currents blocker	200.98 mM	21187-98-4	3 years -20°C powder 2 years -80°C in solvent

NAME	STRUCTURE	Indication FDA / méca connu	DMSO Solubility mM	CAS No	STORAGE
Glyburide		antidiabetic sulfonylurea derivative (binds to the sulphonylurea receptor (SUR1) and blocks ATP-sensitive potassium channels, lead-ing to the release of insulin)	200.4 mM	10238-21-8	3 years -20°C powder 2 years -80°C in solvent
Propranolol hydrochloride		non-selective beta-adrenergic receptors inhibitor	199.45 mM	318-98-9	3 years -20°C powder 2 years -80°C in solvent
Ranitidine		histamine H2-receptor antagonist (stomach or intestinal ulcers)	199.5 mM	66357-59-3	3 years -20°C powder 2 years -80°C in solvent
Ketoconazole		Antifongique	9.4 mM	65277-42-1	3 years -20°C powder 2 years -80°C in solvent
Propranolol hydrochloride		non-selective beta-adrenergic receptors inhibitor	199.45 mM	318-98-9	3 years -20°C powder 2 years -80°C in solvent
Ribavirin		guanosine analogue traitement infections chroniques HCV	200.64 mM	36791-04-5	3 years -20°C powder 2 years -80°C in solvent
Propranolol hydrochloride		non-selective beta-adrenergic receptors inhibitor	199.45 mM	318-98-9	3 years -20°C powder 2 years -80°C in solvent
Ganciclovir		inhibitor of the Herpesvirus (CMV)	105.78 mM	82410-32-0	3 years -20°C powder 2 years -80°C in solvent

nM Range
nM-µM Range
µM Range
µM-mM Range
mM Range

To more visibility the table has been simplified



CONCLUSIONS

The creation of an **evolving database** will make it possible to better identify the ranges of “screening concentration” by taking into account the maximum amount of information collected (Toxicity, cellular models, median dose efficiency...).
Thus I-stem will be able to create **a customized library of repositionable compounds** that can be screened in different ways, depending on the pathology studied, increasing the chances of identifying a potential drug for orphan but also ultra-rare diseases.