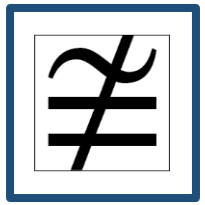
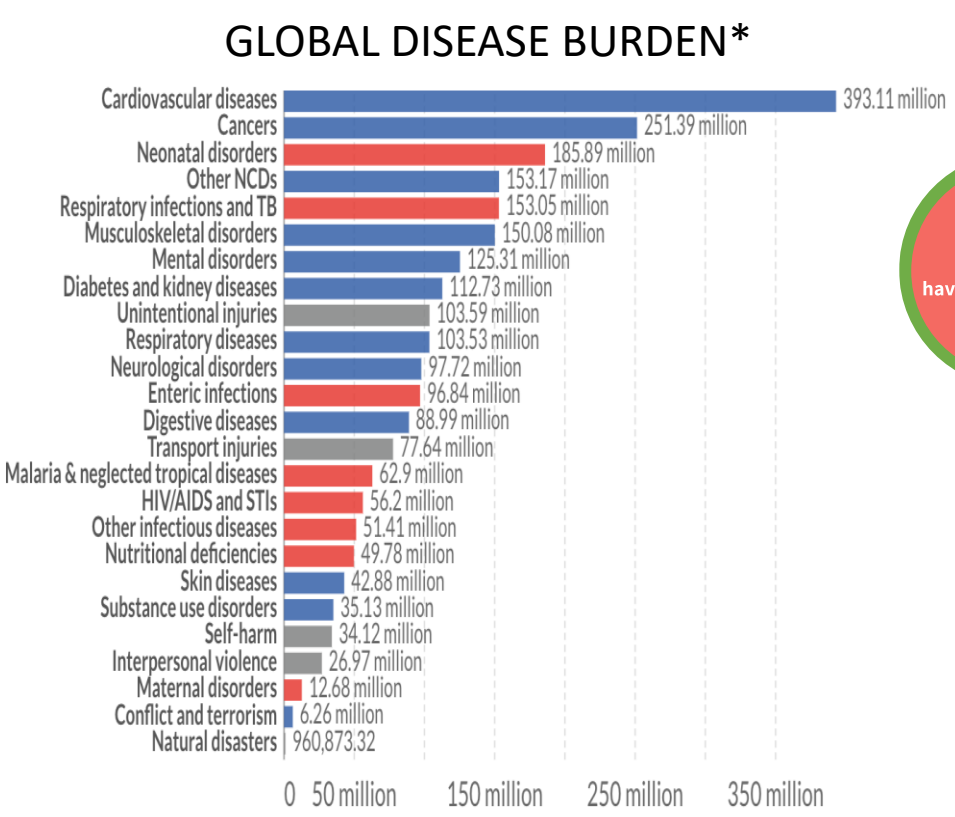
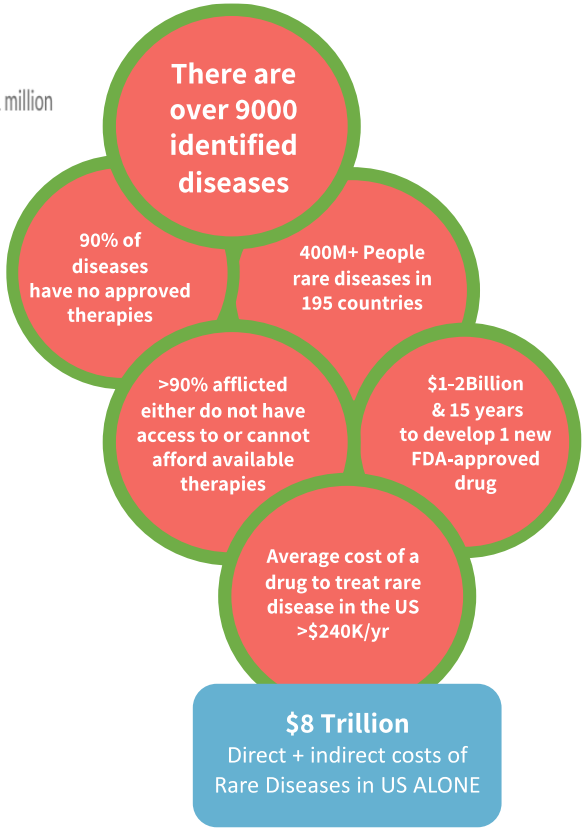


# DRUG REPURPOSING : AN ENIGMA

I am always doing that which I cannot do, in order that I may learn how to do it. — Pablo Picasso

# MORE THAN 9000 DISEASES HAVE NO THERAPIES

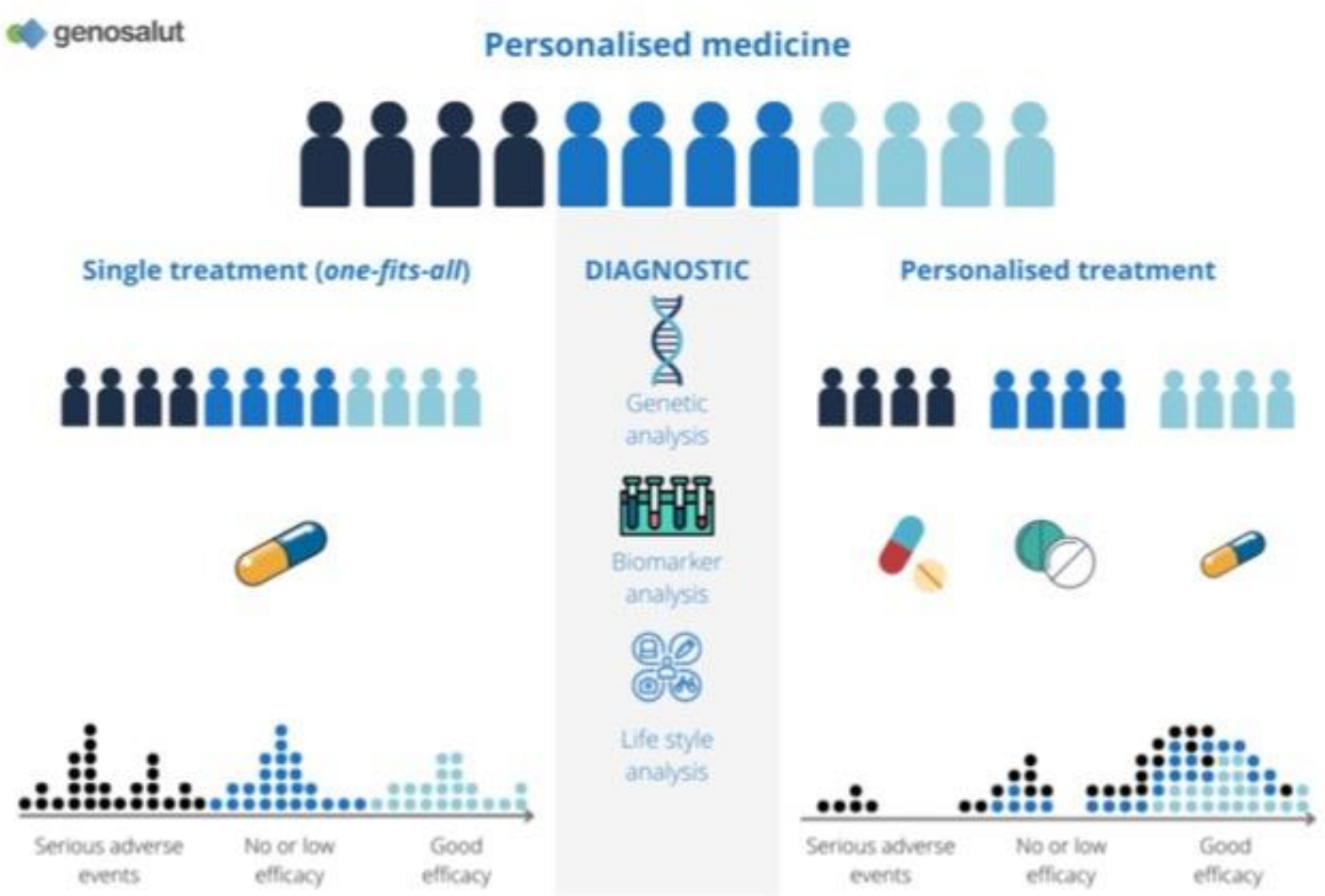



- **Current Drug Discovery and Development (DDD) model cannot address the crisis:**
  - **Resources at current cost**
  - **A model in place since the 1960s**
  - **Alignment and incentives**
  - **Capacity**

*Development of tailored therapies will require a millennia if done de novo, drug repurposing may provide a solution – perhaps is the only viable solution*

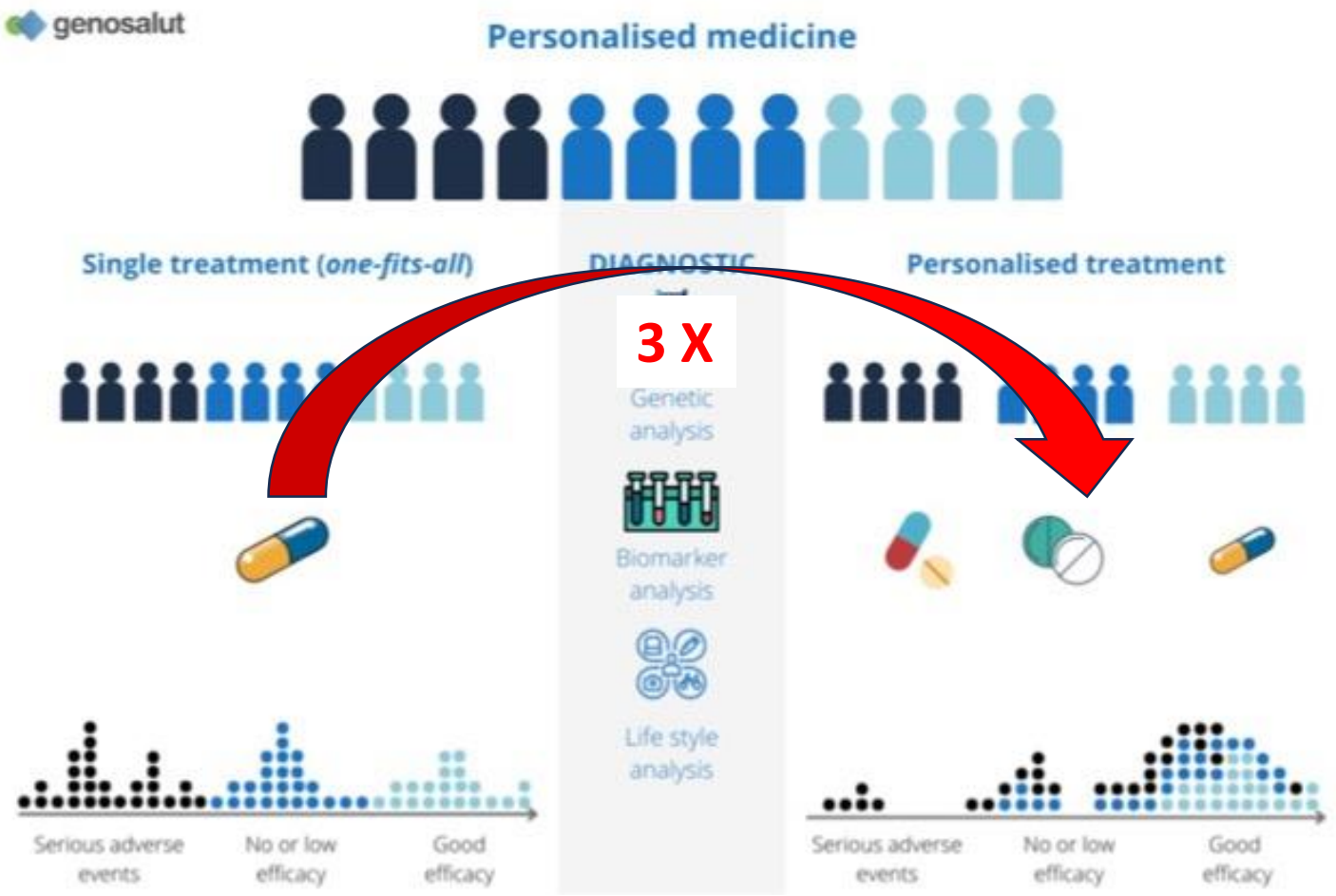
# PERSONAL MEDICINE – ADDING TO THE NEED




**Precision** medicine uses molecular and genetic information to guide treatment decisions

**Personalized** medicine is the next step to develop therapeutics to help create an individualized healthcare plan

# INCREASING THE CHALLENGE




As each therapeutic indication is sub-divided one will need more therapeutics per indication

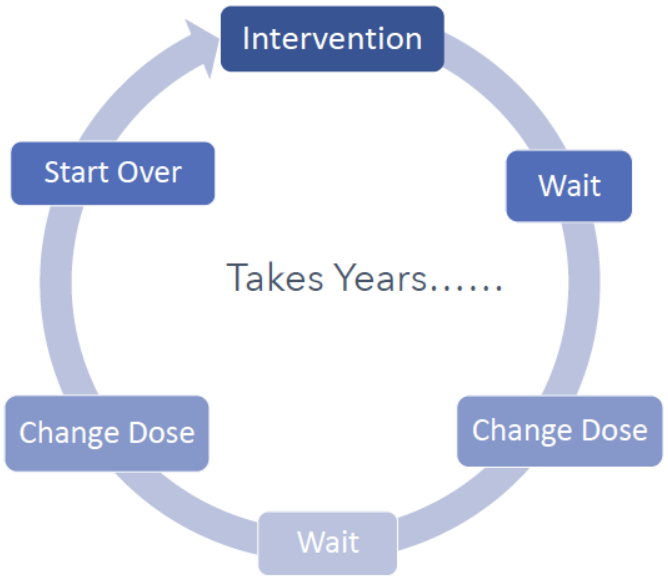
NEED TO DEVELOP MORE THERAPEUTICS → $$ $$ &

**At current cost of >$2B & >12 yr per therapy there is not enough money OR time to address even a fraction of the >9000 diagnosed diseases**

***DRUG REPURPOSING PERHAPS IS THE SOLUTION***

# N-OF-ONE MEDICINE AT CORE OF PERSONAL MEDICINE

- Understanding of human biology is inadequate. leading to trial and error
- Individual therapeutic response ≠ Group based outcome of a randomized controlled trial
- Clinical trials use instruments, devices or tests not practiced in the clinic
- Rare diseases well suited – no therapies and heterogenous patient population
- Improve patient care by understanding of complexities of human biology.




*Wilmont et al https://doi.org/10.1080/17482631.2024.2318810*

# REASONS TO REVAMP THERAPEUTIC DEVELOPMENT

- Continuing and compelling need for treatments globally (affordable)
- Lack of a robust cost-effective pipeline of products in discovery and development
- Development dictated primarily based on poor and unreliable financial analyses
- Pharma's failure to deliver **cost-effective drugs** to patients
- Drug repurposing can enhance translational research for new therapies
  - Significantly lower to >$2B cost of de novo DDD drug
  - 5-6 years compared to 10-12 years for conventional DDD
  - Success rate >80% compared to ~10%
  - Personalized/precision medicine requiring a better, cheaper and effective therapies.
  - Impact orphan, rare and neglected diseases, provide therapeutics where none existed
- Impact of Drug Repurposing (DRPx) can be real and sustainable

**ROADBLOCK IS EXCLUSIVITY/IP**

# INTELLECTUAL PROPERTY ISSUES

- Impaired patenting of new use and/or enforcement
- Information in public domain can affect novelty and consequently patentability
- Repurposing uses in clinical practice as off-label, non-registered uses
- Available strengths and dosage forms are compatible for new indication
- Some legislations impede obtaining a patent for second or further medical uses.
- In EU/US there is data protection/market exclusivity if new indication is by the originator and not available to non-originators

- Solution - new indication requires nonmarketed strengths (preferably lower) or a new formulation.
- Newer derivatives are the best option, but changing the drug molecule implies stepping away from the repurposing strategy.

# LADR$^4$ – A PLATFORM TECHNOLOGY

- A platform that can help **r**epurpose, **r**eprofile, **r**epositions or **r**escue drugs
- LADR$^4$ improvements include:
  - Enhanced absorption by eliminating the solubility barrier to absorption
  - pH independent solubility resulting improved PK
  - Improved PK can result in an improved PD profile
  - PK properties are tunable
  - Differential dosing and possibility for alternate route of dosing
  - Efficient, cost effective
  - **Fo the first-time provides composition of matter protection for repurposed drugs**
- Applicable to many chemotypes, resulting in increased solubility, and a patentable NCE.
- The approach has been assessed and validated under the following:
  - IP –issuance of patents on compounds based on the technology across multiple IP jurisdictions
  - Regulatory – filings with the USFDA/MHRA
  - Commercial – multiple licensing/partnering deals

# LADR$^4$ IS A DIFFERENTIATED PRO-DRUG APPROACH

| | Typical Pro-Drug Approach | LADR$^4$ Pro-Drug Approach |
|---|---|---|
| Patentability | NCE | NCE |
| PK | Empirical | Ability to tune AUC, $C_{max}$, MRT |
| ADME | Affected | Same as original drug |
| Exposure | Generally systemic | Negligent (iv), None (po) |
| Pharmacology | Affected | Not affected |
| Applicability | Limited | Generally applicable |
| Regulatory | Standard dev. path | 505(b)(2)* path |
| Solubility | Unpredictable | Inc. & non-pH dependent |
| Variants | Often single | Multiple Options |

* May require a few additional pre-clinical studies

# LADR[4] CONSEQUENCE ON DRUG REPURPOSING

| PIPELINE | EXCLUSIVITY | SUPERIORITY | SPEED |
|---|---|---|---|
| Applicability to wide chemotypes. Rapid time to development compound | COM patent valid for 20 years for generic drugs | Improved bio-availability, & efficacy in new indications | 505(b)2 path to expedite time and reduced resources needed to obtain FDA approvals |

**3-4X FASTER**

- **3-5 years vs 12-15 years for DDD***

**50X CHEAPER**

- **<$50M vs >$2B for DDD**

**10X BETTER Success Rates**

- **>80% vs <10% for DDD**

* **DDD = *de novo* Drug Discovery & Development**

# TRANSITION TO PERSONAL THERAPEUTICS

| | OLD | NEW |
|---|---|---|
| Product Portfolio | Narrow | Wide |
| Markets | Mass Phenotype | Targeted Genotype |
| Patient Focus | Disease state | Disease life cycle |
| Treatment | 1 Drug / 1 Disease | Continuity of treatmentS |
| Manufacturing | Few large runs | Many small runs |
| Sales | Generalized | Focused |
| Economics | Scale | Knowledge |


OLD PHARMA APPROACH

- Time: 10-13 years
- Cost: >$2 billion
- Success: ~10%

NEW PHARMA APPROACH TO

- Time: 3-5 years
- Cost: <$100 million
- Success: >80%

# FINANCIAL PERSPECTIVE

| | DDD | DRPx | LADR[4] |
|---|---|---|---|
| AVERAGE TIME TO APPROVAL | 13.5 yr | 6.5 yr | <5yrs |
| AVERAGE COST TO APPROVAL | >$1B | ~$300M | <$50M |
| SUCCESS RATE | | | |
| Discovery | <10% | 100% | 100% |
| Phase II to Launch | 10% | 25% | >25% |
| Phase III to Launch | 50% | 65% | >65% |
| FINANCIAL ANALYSIS* | | | |
| NPV @$300M Annual Sales | -$795M | $280M | >$280M |
| NPV @$2B Annual Sales | $776M | $4.8B | >4.8B |
| IRR @$300M Annual Sales | -3.2% | 15% | >15% |
| IRR @$2B Annual Sales | 15.6% | 43.6% | >43% |
| FASTER BREAK-EVEN | $1.2B | $195M | <$195M |

Overall

- High success rate – lower risk
- Shorter time to market
- Very low cost to develop
- Lower break-evens
- Higher IRR's

* @estimated 10% cost of capital

# LADR[4] APPLICATIONS

- Generics
- Active metabolites
- Natural products
- Pediatric formulations
- Changing route of dosing
- Improving tolerance and efficacy
- ….

- Mitochondria depletion and dysfunction
- Oncology
- Cardiovascular
- Muscle
- Neurodegeneration
- Inflammation
- Pain/Anesthesia
- …….

# LADR[4] EFFECT ON SOLUBILITY : PACLITAXEL

SOLUBILITY - HPLC

| | SOLVENT | | | |
|---|---|---|---|---|
| Compound | Normal Saline | 5%DMA/ Normal Saline | 9% NMP/ Normal Saline | 5% DMSO/ Normal Saline |
| Paclitaxel | 0.1μg/mL[1] | Not Soluble | Not Soluble | Not Soluble |
| PAC_LR | >500μg/mL | ~1mg/mL | >1.5mg/mL | >1.2mg/mL |

- PAC_LR increase in solubility
  - >5000X in normal saline
  - >10,000X in normal saline/5%DMA
  - >12,000X in normal saline/5%DMSO
  - >15,000X in normal saline/9%NMP

- **PAC_LR IS ORALLY ABSORBED WITH NO OVERT GI TOXICITY**

1. Kono et al., J. Bio. Materials Research, Part A, 2003

# LADR[4] EFFECT ON PK/PD

*Dose: 3mg/Kg or 3mg/Kg equivalent oral dose in rat*

| PK parameters | Nico | NICO_LR1 | NICO_LR2 |
|---|---|---|---|
| Cmax (µM) | 7.8 | 6.6 | 9.1 |
| Tmax (min ) | 70 | 110 | 70 |
| AUC (µM*hr) | 20.4 | 28.5 | 46.4 |
| $t_{1/2}$ (hr) | 3.43 | 4.85 | 3.67 |

**NICO_LR1**

AUC ↑ 40%

Cmax ↓ 15%

**NICO_LR2**

AUC ↑ 127%

Cmax ↑ 17%


- **IMPROVED PK PROFILE HAS TRANSLATED TO PD EFFECTS NOT SEEN BY NICO.**
- **COMPOSITION OF MATTER IP ISSUED**

*Dose: 10 mg/Kg or 10 mg/Kg equivalent oral dose in rat*

| Parameters | MMF | MMF_LR |
|---|---|---|
| Cmax (nM) | 53976 | 43559 |
| Tmax (h) | 0.16 | 0.33 |
| AUC (nM.h) | 24435 | 54522 |
| T1/2 (h) | 1.60 | 5.89 |

**MMF_LR**

AUC ↑ 123%

Cmax ↓ 19%


- **IMPROVED PK PROFILE MMF_LR TRANSLATED TO PD EFFECT NOT SEEN BY MMF**
- **COMPOSITION OF MATTER IP ISSUED**

# TUNING PHARMACOKINETICS

| Compound | $T_{max}$ (hr) | $C_{max}$ (nM) | AUC (nM*hr) |
|---|---|---|---|
| INIB | 2.00 | 323.3 | 1753 |
| INIB-LR1 | 2.00 | 433.2 | 2412 |
| INIB-LR2 | 2.00 | 332.5 | 2712 |
| INIB-LR3 | 2.00 | 496.7 | 3328 |
| INIB-LR4 | 2.00 | 420.0 | 3623 |
| INIB-LR5 | 4.00 | 208.3 | 1559 |
| INIB-LR6 | 4.00 | 168.8 | 1418 |
| INIB-LR7 | 4.00 | 131.4 | 1477 |
| INIB-LR8 | 4.00 | 171.3 | 1503 |
| INIB-LR9 | 2.00 | 138.9 | 1043 |
| INIB-LR10 | 2.00 | 231.8 | 1898 |
| INIB-LR11 | 2.00 | 395.9 | 3115 |
| INIB-LR12 | 2.00 | 163.7 | 1705 |
| INIB-LR13 | 4.00 | 71.5 | 483 |

# EFFECT ON PHARMACOKINETICS

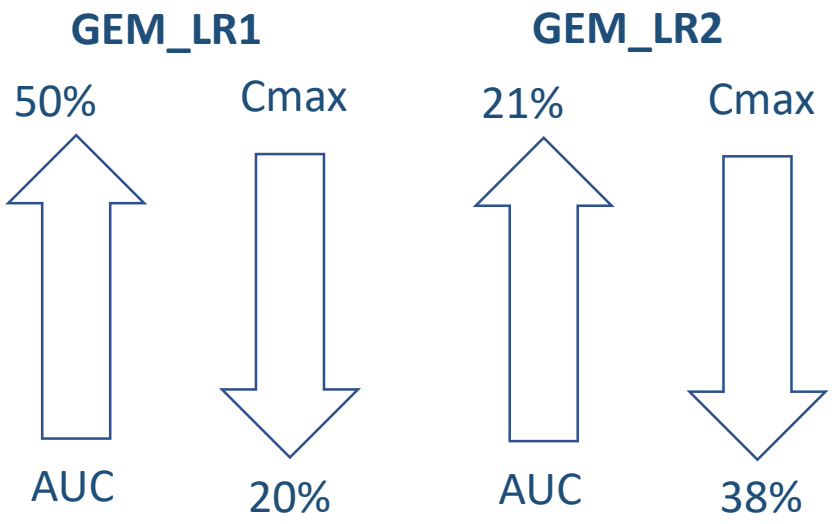
*Dose: 3mg/Kg or 3mg/Kg equivalent oral dose in rat*

| Parameters | ICLO | ICLO_LR |
|---|---|---|
| Cmax (nM) | 32.86 | 309.13 |
| Tmax (h) | 1.58 | 1.00 |
| AUC (nM.h) | 56.25 | 638.56 |

9.5 fold increase in Cmax
11.4 fold increase in AUC

*Dose -10 mg/Kg or equivalent dose in mice*

| PK parameters | GEM | GEM_LR1 | GEM_LR2 |
|---|---|---|---|
| Cmax (nM) | 5816 | 4631 | 3600 |
| Tmax (hr) | 0.3 | 0.2 | 0.4 |
| AUC (nM*hr) | 3557 | 5317 | 4301 |

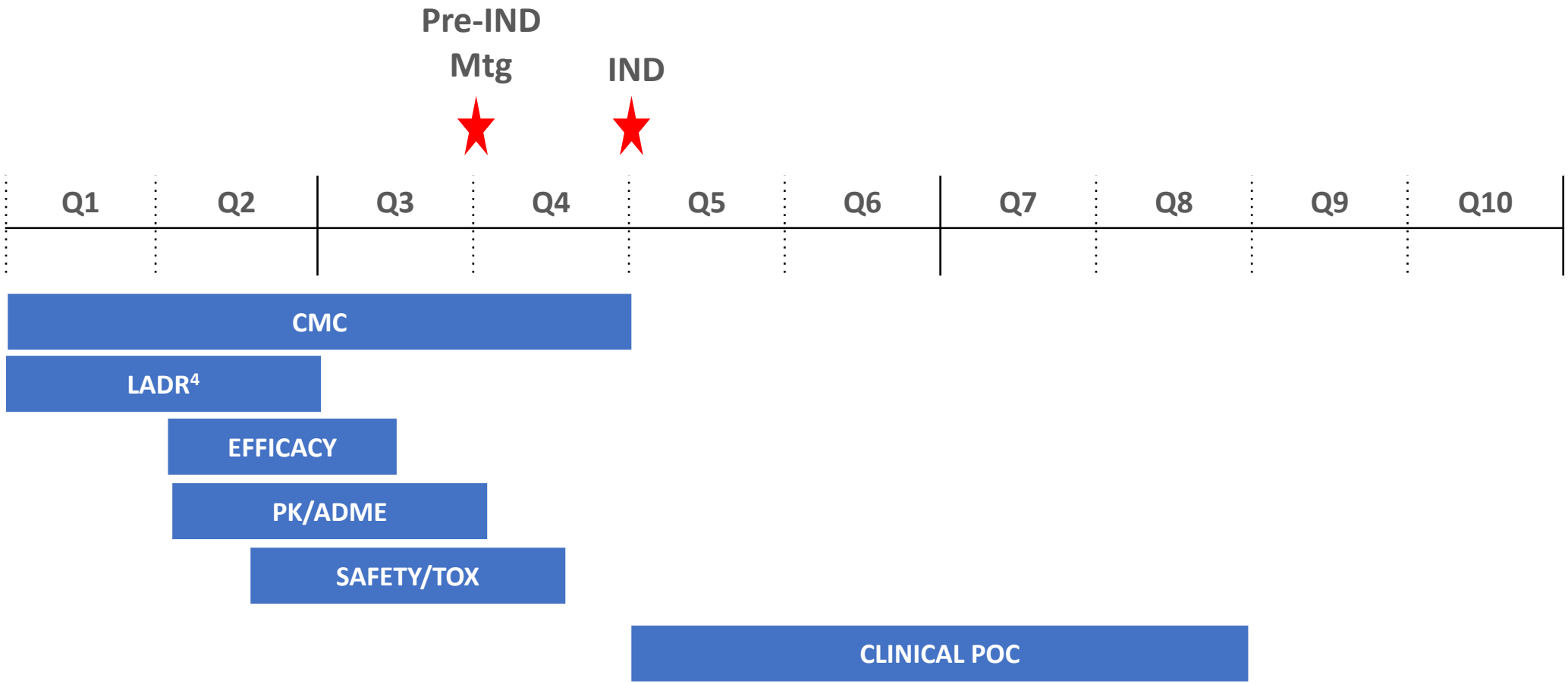


# DEVELOPMENT CANDIDATE SELECTION


| SYNTHESIS | STABILITY & CONVERSION | SINGLE PK STUDY | DOSE RANGING PK | MULTIPLE DAY PK |
|---|---|---|---|---|
| •Synthesis of 6-8 analogs<br>•Solubility assessment | • Chemical stability<br>• Conversion to parent in rat plasma and whole blood at (0, 15, 30, 60, 120 mins) | • $C_{max}$, $T_{max}$, $T_{1/2}$, AUC | • 3 Doses | • 7-14 day study to ascertain dose tolerability and dose accumulation<br>• Gross observational effect on GI, liver and kidney |
| 4-6 weeks | 2-3 weeks | 2-3 weeks | 3-4 weeks | 2 weeks |

**~4-6 MONTHS**

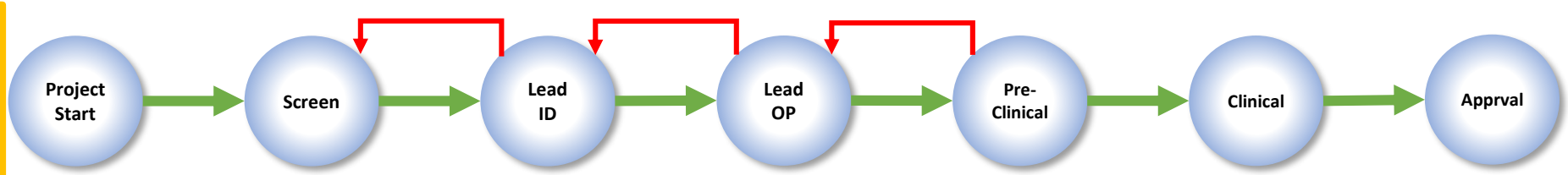
# DEVELOPMENT TIMELINE TO CLINICAL POC



# A NEW THERAPEUTIC DEVELOPMENT STRUCTURE

PHARMACEUTICAL INDUSTRY'S MODEL FOR DEVELOPING NEW THERAPEUTICS HAS NOT CHANGED SINCE INCEPTION OF THE MODERN PHARMACEUTICAL INDUSTRY AS IT IS PRIMARILY FOCUSED FOR DEVELOPED COUNTRIES

**10-12 YR, HIGH RISK, HIGH COST**




TRANSFORM


**3-5 YR, LOW RISK, LOW COST**

# IN CONCLUSION

- Drug repurposing needs to be a significant approach in the pharmaceutical sector to address many unmet needs.
- Drug repurposing is a crucial strategy for rare and neglected conditions
- It can provide significant financial and societal returns.
- Systems and precision medicine can significantly enhance prospects for drug repurposing
  - Systems pharmacology for poly pharmacology to treat complex disorders
  - Precision medicine for characterization, understanding, and classification of disease
- **LADR$^4$ can be a path to unlock the value of drug repurposing.**