



motif

## The Lead Hopping Discovery Engine

**Zaki Hosny**  
Chief Executive Officer



# The Lead Hopping Discovery Engine

- Moving Drugs from First in Class to Best in Class
- Discovering New Drugs from Proven Targets
- Fulfilling the basic need of Big Pharma
- Fast Discovery to Proof of Concept in Man
- Motif is driven by a team from Big Pharma
- The Motif team has done it before

# A stellar drug discovery track record

- US patents issued: 246
- Pre-clinical candidates: > 210 novel small molecules & peptides
- Clinical drug candidates: Type 1 & 2 diabetes, hepatitis C, CINV, COPD, cystic fibrosis, hypertension, heart failure, obesity, cancer



\$5.6bn



\$2.3bn



\$1.9bn



Prinivil  
\$1.7bn



\$1.3bn



\$3.6bn



\$0.3bn



\$2.1bn



\$2.2bn



\$1.2bn

Registered trademarks & logos of respective companies

# Lead hopping: launching pad in drug discovery

## Big pharma

Target discovery/validation  
Assay development  
High throughput screening  
In vitro/ In vivo assays  
Lead optimization  
Pre-clinical development  
POC in man



Validated target?  
POC in man?  
Tractable chemistry?  
Potential clinical differentiation?  
IP freedom to operate?

## First in Class to Best in Class

Develop optimal structure for Best in Class compound



Multiple analog development ↔ biology assays



Pre-clinical development: toxicology; PKDM, in vivo pharmacology

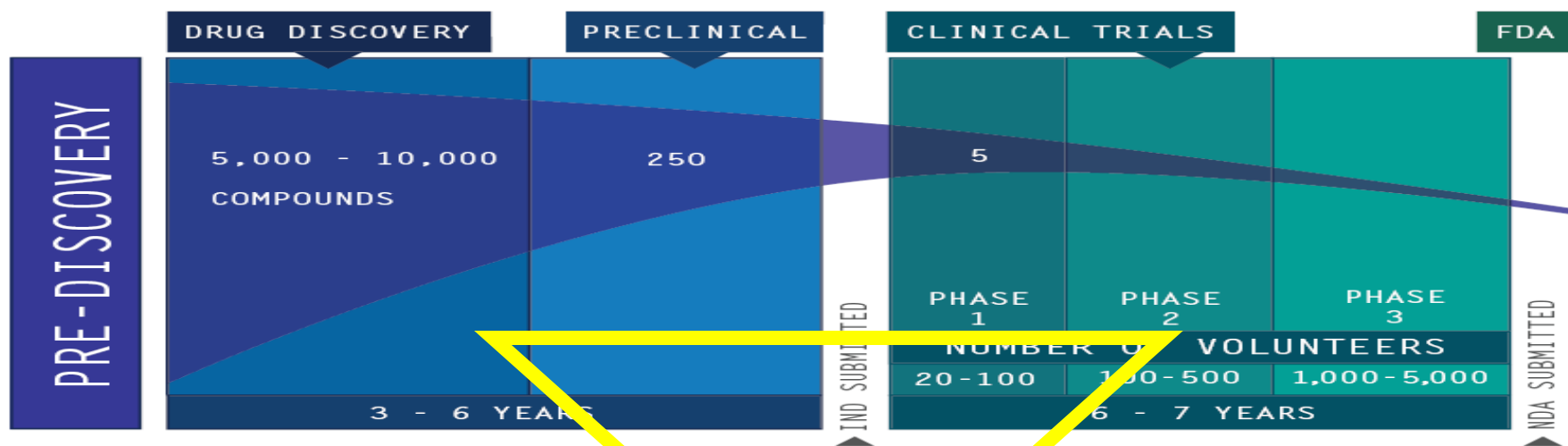


POC in man



License out Best in Class NCE with POC in Man to Pharma after Phase IB/IIA

# Lead hopping: the sweet spot in drug discovery



- Lead hopping & optimization from pharma IP
- Develop customized best in class pre-clinical candidates & file IP.
- Pre-clinical development: animal toxicology & pharmacology; formulation development
- Phase I A: IND for first in man studies : acute safety profile; dosage spectrum incl. maximum tolerated dose
- Phase 1 B / II A : Proof of efficacy, safety & optimum dosage in patients

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# First in class to best in class: a validated model



STATINS: Lovastatin: Atorvastatin

- Improved human pharmacokinetic profile. Greater efficacy & dosage convenience



ACE INHIBITORS: Captopril: Enalapril / Lisinopril

- Structurally- based adverse effects minimized. Improved pharmacokinetics; Once daily dosing



CA CHANNEL BLOCKERS: Nifedipine: Amlodipine

- Improved pharmacokinetic profile. Improved safety & tolerability



AZOLES: Myconazole: Voriconazole

- Non-orally available to oral



ARBs: Losartan: Valsartan

- Improved pharmacokinetic profile.



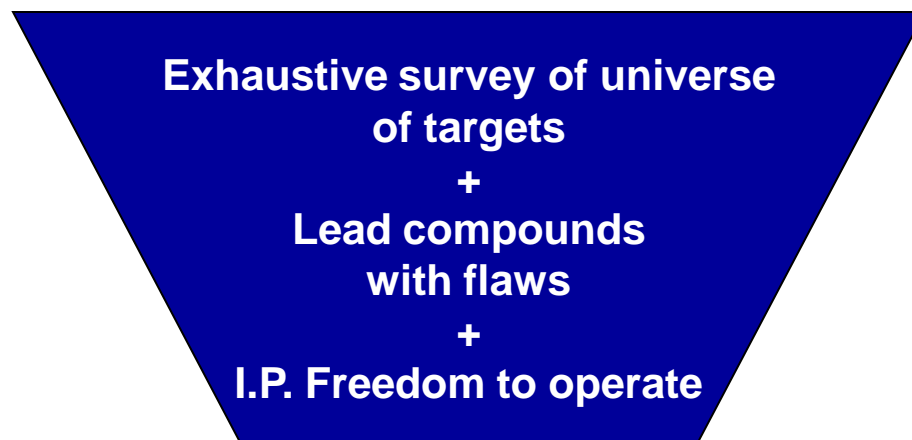
QUINALONES: Norfloxacin: Ciprofloxacin

- Limited tissue penetration. Systemic penetration

# Motif – distinctive & de-risked

- No speculative projects: **ONLY** validated targets; mechanisms proven in man; lead-hop from first in class small molecules with known profiles & defined, correctable flaws
- De-risked in execution: quick to measure clinical end-points (clinical trials  $\leq$  1month duration); validated biological paradigms; published assays
- De-risked at back end for partners: Phase III probability of success significantly higher with proven mechanisms
- Business model not dependent on downstream revenue

# Best in Class - New Drug Candidates



| Projects                       | Validated Target | POC in Man | Tractable Chemistry | Clinical Differentiation | I.P. Freedom |
|--------------------------------|------------------|------------|---------------------|--------------------------|--------------|
| MTF 001 / Obesity              | ✓                | ✓          | ✓                   | ✓                        | ✓            |
| MTF 002 / MRSA                 | ✓                | ✓          | ✓                   | ✓                        | ✓            |
| MTF 003 / Migraine             | ✓                | ✓          | ✓                   | ✓                        | ✓            |
| MTF 004 / Over Active Bladder  | ✓                | ✓          | ✓                   | ✓                        | ✓            |
| MTF 005 / Rheumatoid Arthritis | ✓                | ✓          | ✓                   | ✓                        | ✓            |

# Motif Drug Candidates versus Lead Compounds

- Project A: disease undisclosed. Greatly increased receptor selectivity; significantly improved dosage flexibility to yield greater efficacy and safety margin; QD dosage
- Project B: disease undisclosed. Increased potency & improved brain / blood drug exposure ratio to improve safety profile & enhance efficacy
- MTF 002: MRSA. Significantly reduced off-target activity; comparable intrinsic potency; expanded therapeutic window; oral and IV dosing for hospital and community acquired infections

# Dynamic Discovery Process

## MOTIF

Define biological activity & liabilities of FIC compound

Define optimal structure of BIC compound 

Select & refine analogs 

Select analogs for biological assays of target engagement / modulation 

Select & refine analogs 

## DISCOVERY PARTNER

Develop chemical analogs per spec

Iterate chemical analogs

Conduct biological assays

Iterate chemical analogs

- **Highly iterative process: 40 analogs / month / project**
- **Optimized structure: File IP**

Define toxicology, PK, drug metabolism, pre IND 

Conduct studies

**File IND application**

Define Proof of concept study

Conduct studies 

**POC**

# A progressive model: funding, IP, assets

| Months   |                   | 18                 | 36           | 48  |
|----------|-------------------|--------------------|--------------|-----|
| Projects | Biology/Chemistry | Pre-Clinical / IND | Clinical/POC |     |
| MTF 001  |                   | P                  | IND          |     |
| MTF 002  |                   |                    |              |     |
| MTF 003  |                   | P                  | IND          | POC |
| MTF 004  |                   | P                  | IND          | POC |

|         |  |   |     |     |
|---------|--|---|-----|-----|
| MTF 005 |  | P | IND | POC |
|---------|--|---|-----|-----|

P Patent App & PCC   
 IND Investigational new drug application   
 POC Proof of concept

# Leverage outsourcing to minimize burn

- Medicinal chemistry, biology, pharmacology, toxicology, pharmacokinetics/ drug metabolism out-sourced to specialist companies in Asia & Europe
- Minimize fixed costs
- 4 projects simultaneously plus pipeline
- 10-12 FTE scientists per project
- Operational flexibility within & across projects
- Advanced discussions with leading companies in field

# Business model: key milestones & assumptions

- Start MTF 001, MTF 002, MTF 003, MTF 004 in Yr 1
- Timeline: project start to Proof of Concept in Man in 4 years
- Month 18 : Pre Clinical Candidates / Provisional Patent Application
- Month 36: IND ready
- Month 48 : Proof of Concept in Man
- License out 1 Pre Clinical Candidate in Yr 3 : \$15 - 20M
- Revenue: fund development to Proof of Concept on 3 compounds; start early chemistry/ biology on 1- 2 new projects
- License out 1 compound with Proof of Concept in Man in Yr 5: \$70M

# Average upfront value of POC deals: \$70-75M

Amgen / Array Biopharma (12/09): Ph I \$60 million upfront  
Glucokinase activator for Type 2 diabetes

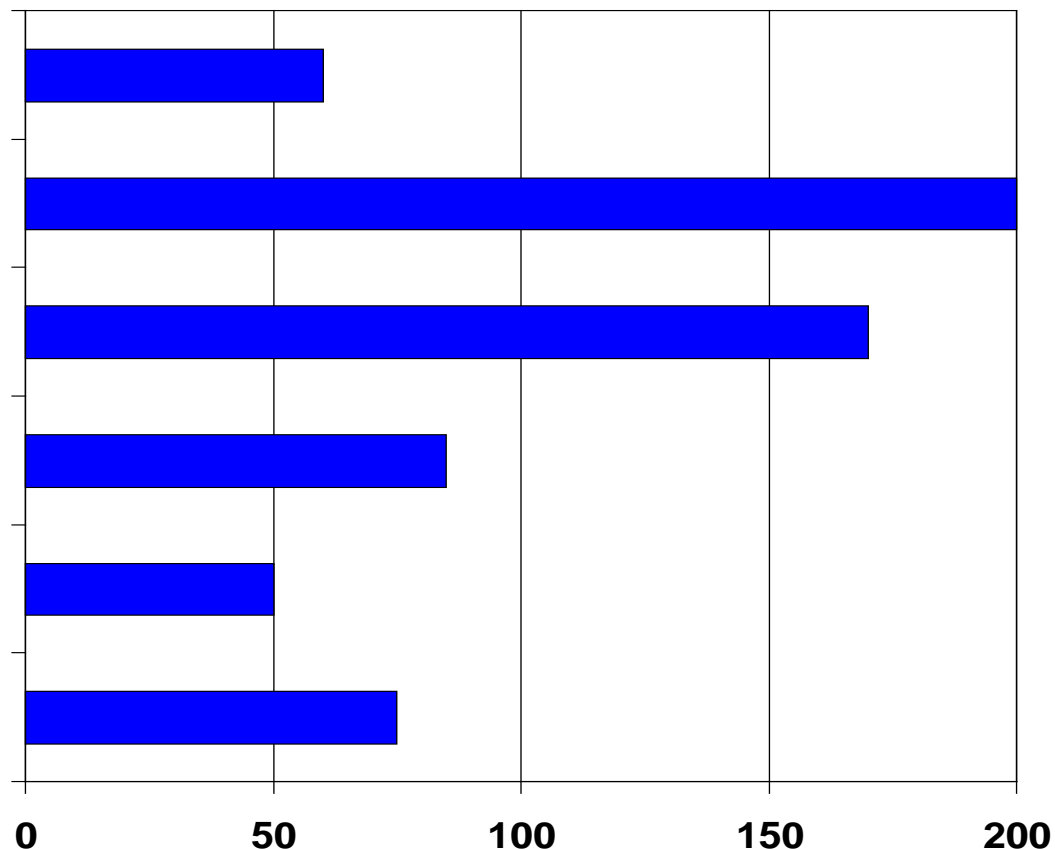
AstraZeneca / Targacept (11/09): Ph II \$200 million upfront  
TC5214 for depression

Abbott / PanGenetics(11/09): Ph I \$170 million upfront  
nerve growth factor for osteoarthritis /pain

BMS /Alder (11/09): Ph II A \$85 million upfront  
novel biologic for rheumatoid arthritis

Merck / Portola (7/09): Ph II \$50 million upfront  
Betrixaban: anticoagulant

Novartis / Portola (2/09): Ph II \$75 million upfront  
Elinogrel : antiplatelet



\$M

# The “A” Team from Big Pharma

## Top Company Experience

**Merck, Schering Plough, Wyeth, GSK, Bayer**

### Drug Discovery

John Amatruda M.D

James N. Livingston Ph.D

### Drug Metabolism & Pharmacokinetics:

Gerald T. Miwa, Ph.D: 32 yrs

Biology: James N. Livingston Ph.D: 17 yrs

Clinical: John M. Amatruda, M.D: 17 yrs

Computational Chemistry: Simon K. Kearsley Ph.D: 20 yrs

Intellectual Property: P.S. Kalyanaraman, Ph.D., J.D: 20 years

### Medicinal Chemistry

Malcolm MacCoss, Ph.D., FRSC: 28 yrs

Matthew J. Wyvratt, Ph.D: 32 yrs

Mark L. Greenlee, Ph.D: 26 yrs

Jerauld S. Skotnicki, Ph.D: 30 yrs

Pharmacology: Euan McIntyre: 24 yrs

Toxicology: James S. MacDonald, Ph.D: 31 yrs

# A stellar drug discovery track record

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# The Lead Hopping Discovery Engine

- Pharma A team with proven track record in drug discovery and lead hopping
- Discovery engine for best in class compounds with de-risked model
- Rigorous selection criteria - boosting probability of success
- Small company culture, big pharma discipline



motif

## The Lead Hopping Discovery Engine

Zaki Hosny  
Chief Executive Officer



# The Motif Team

## Management

Richard Morgan: Chairman, Co-founder & former Director, Celgene

Zaki Hosny: CEO, 35 years at Merck & Co.

## Drug Discovery

Matthew Wyvratt Ph.D, SVP, Drug Discovery

Mark Greenlee Ph.D, Exec. Dir, Medicinal Chemistry

Jerauld Skotnicki Ph.D, Exec. Dir, Medicinal Chemistry

Simon Kearsley Ph.D, Exec. Dir, Computational Chemistry

Malcolm MacCoss Ph.D

James Livingston Ph.D

James MacDonald, Ph.D

Euan MacIntyre, Ph.D

John Amatruda, M.D.

Gerald Miwa, Ph.D

P. Kalyanaraman, Ph.D.

Bruce Williams