Effect of Approved Non-Oncology Drugs on the Metastatic Process: Risks & Benefits

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Background

- Most drugs approved for metastatic cancer either treat the secondary tumour's proliferation or influence immunity.
- None of them delays the process of metastasis or has any effect on the pathophysiology of metastasis[1].
- As a result, overall and progression-free survival of solid tumour patients have improved only by 2.8 and 3.3 months over the last decade[2].
- Therefore, It is imperative to identify drugs that would effectively delay metastasis and be relatively safe to be positioned for neo-adjuvant and adjuvant clinical settings.
- As 90% of cancer deaths are due to metastasis, targeting metastasis in combination with other treatments, should be beneficial in improving the low clinical benefit of existing therapies[3].
- Mestastop took a systems biology-based approach and created three proprietary platforms to identify and progress anti-metastatic compounds.
  1. METAssay® - in vitro, dissects metastasis biology[4]
  2. METSCAN® - ex vivo translation of patient samples[5]
  3. METVivo® - In vivo high throughput animal model[6]

Methods

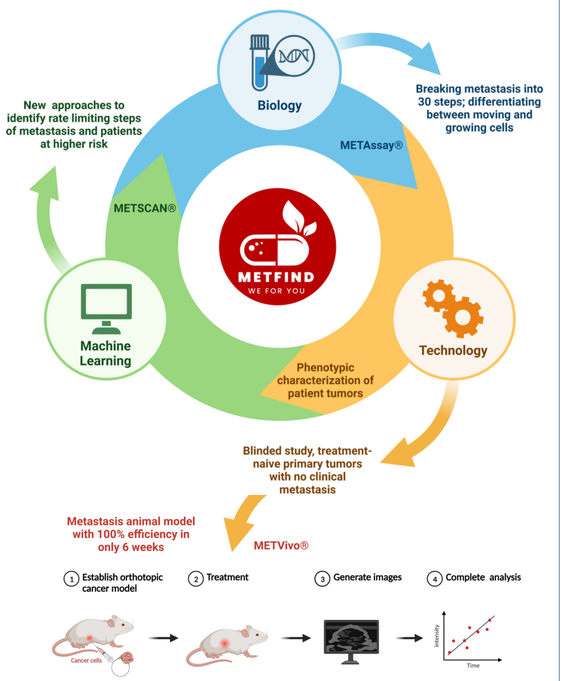


Fig. 1: Schematics of the Mestastop Platforms

Results — Platform Standardization

Fig.2: (A) METAssay® dissects metastasis biology and (B) differentiates between functional properties of growing and moving cells

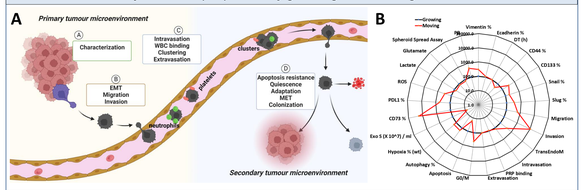


Fig.2: Patients from different tumour types show a similar pattern, (C) CRC & (D) HNC

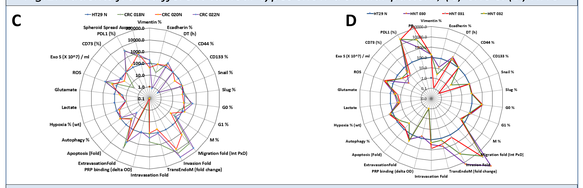
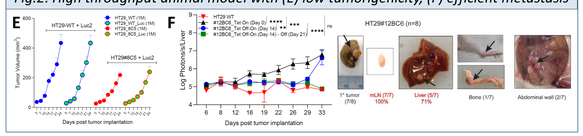


Fig.2: High throughput animal model with (E) low tumorigenicity, (F) efficient metastasis



Result — *In-vitro* to *in-vivo* translation PoC

Fig.3: (A) List of ten approved drugs and their (B) Heat map on key steps of metastasis

A

Code Name	Indications
MS-AP-001	Pain, fever, inflammation
MS-AP-002	Heartburn, peptic ulcer
MS-AP-003	Allergy
MS-AP-004	Hypertension
MS-AP-005	Type II Diabetes
MS-AP-006	Asthma, Allergic Rhinitis
MS-AP-007	Schizophrenia
MS-AP-008	Hypertension
MS-AP-009	Metastatic colon cancer
MS-AP-010	Hypertension

B

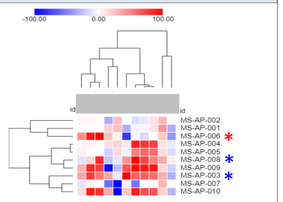


Fig.3: Effect of positive compound AP-003 on (C) patients and (D) in animal model

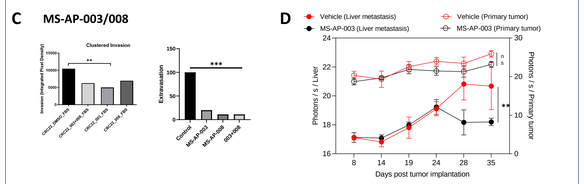
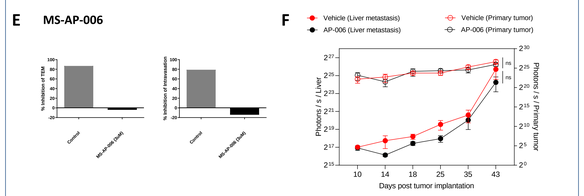


Fig.3: Effect of negative compound AP-006 on (E) patients and (F) in an animal model



Mestastop platforms identify anti-metastatic compounds, with in-vitro to in-vivo PoC

Results — Retrospective Clinical Study

Fig.4: (A) Study Design

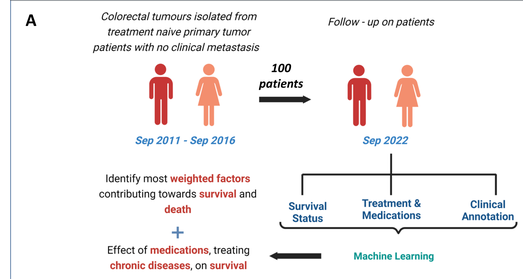
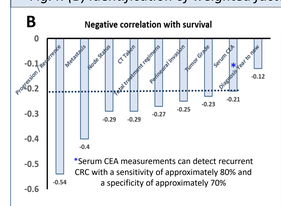


Fig.4: (B) Identification of weighted factors and (C) medicines with impact on survival



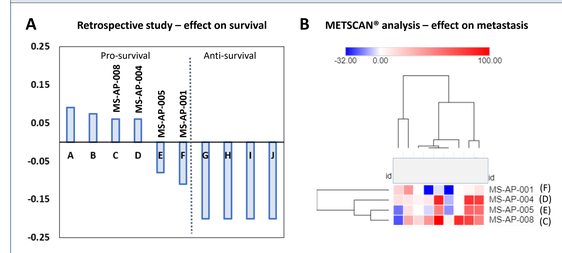
C

Medicine	Null Hypothesis (H0)	Rejects H0 (co-efficient < 0.05)	Co-efficient strength	p-value	Effect on Survival
A	The medications have a negative effect on the survivability of the subject	Yes	-0.33	0.03	Moderately positive
B		Yes	-0.24	0.01	Weakly positive
C		Yes	-0.03	0.046	Weakly positive
D		No	-0.15	0.55	more data required
E		Yes	-0.23	0.03	Weakly positive
F		Yes	-0.005	0.013	Weakly positive
G	The medications have a positive effect on the survivability of the subject	Yes	-0.19	0.03	Weakly negative
H		Yes	-0.31	0.003	Moderately negative
I		Yes	-0.33	0.03	Moderately negative
J		Yes	-0.2	0.01	Weakly negative

Retrospective study confirms effect of non-oncology drugs on survival

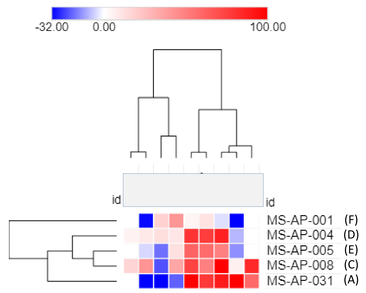
Results — Retrospective trial PoC

Fig.5: Effect of approved drugs in (A) retrospective study survival and (B) METSCAN®



All four drugs identified in patients, picked up by METSCAN®, inhibiting metastasis

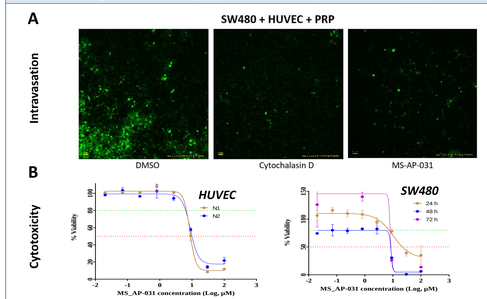
Fig. 6: Analysis of the effect of approved drug A (MS-AP-031), identified by the retrospective study on the METSCAN® platform



METSCAN® rank ordering closely resembles the retrospective study survival data

Results — Cytotoxicity profiling

Fig.7: Inhibition of (A) metastatic steps not due to (B) cytotoxicity



All METSCAN® assays performed at non-cytotoxic concentrations (cell lines & time)

Conclusion

1. METAssay® can successfully triage molecules and identify potent anti-metastasis compounds based on the weighted algorithm of patient-derived METSCAN®
2. The identified compounds translated in the in vivo animal model, METVivo®
3. Retrospective clinical trial of 100 CRC patients suggests that approved non-oncology drugs can impact the survival of primary cancer patients over a follow-up period of five years.
4. Four of these drugs were previously tested in the METSCAN® platform, and rank ordering from the platform almost matched with the retrospective clinical trial data (75%).
5. Further analysis of another compound, Drug A (MS-AP-031), increased the efficiency to 80%.

Next Steps

1. Currently running another retrospective study with 100 head and neck cancer patients
2. Planning for 2000 patient sample retrospective study in Europe and USA
3. Testing more compounds identified by the current study (both with positive and negative impact on survival) on the METSCAN® platform
4. FDA-Approved drug library testing on the METSCAN® platform
5. Identification of potential combinations
6. Fixed dose combination patent followed by clinical trials

References

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