ISTITUTO ITALIANO DI TECNOLOGIA
MOLECULAR MODELING AND DRUG DISCOVERY

UCI School of Medicine

CDC42 Inhibitors: A Class of Drugs that Block Cancer Growth and Metastasis

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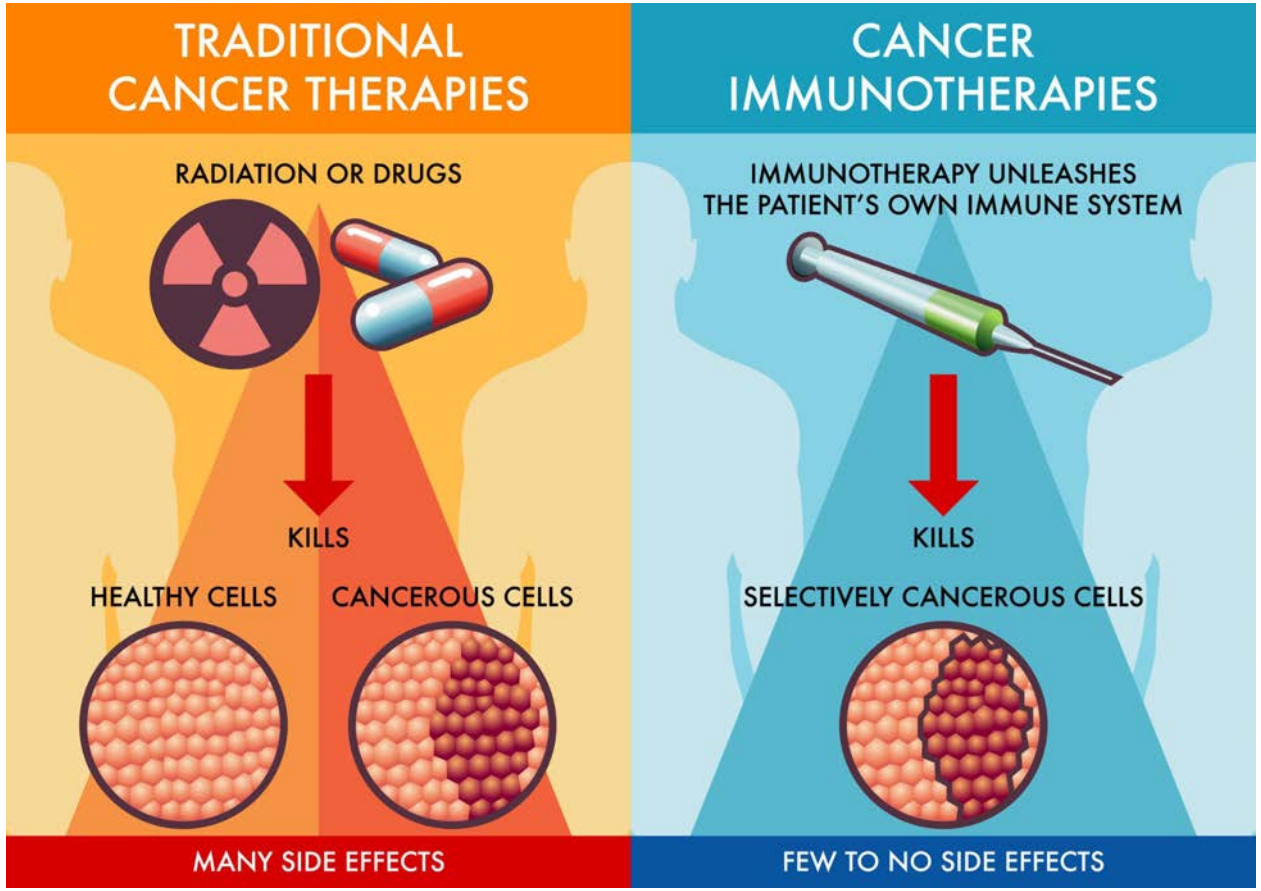
Marco De Vivo, Italian Institute of Technology Genoa

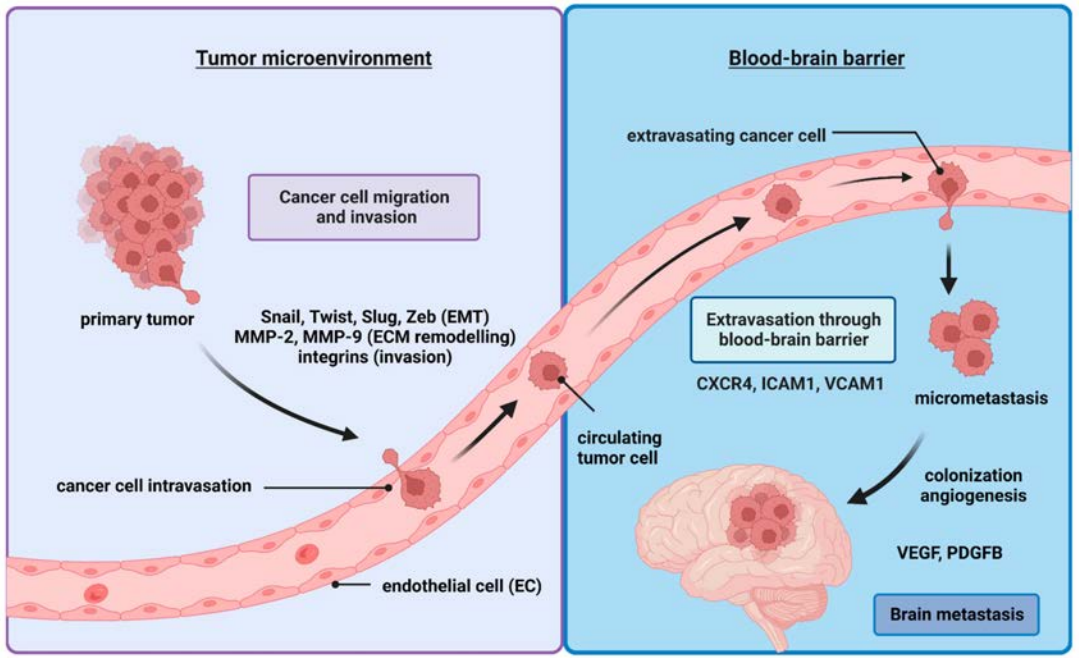
The Problem: There Are No Specific Therapies that Block Cancer Metastasis



WORKS <50% OF TIME

https://www.arizonabloodandcancerspecialists.com/what-is-immunotherapy/

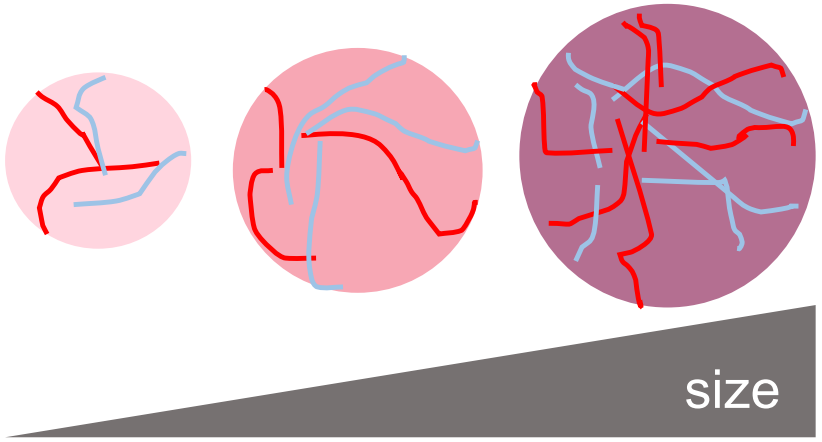
CANCER METASTASIS



Remains a therapeutic "black box"

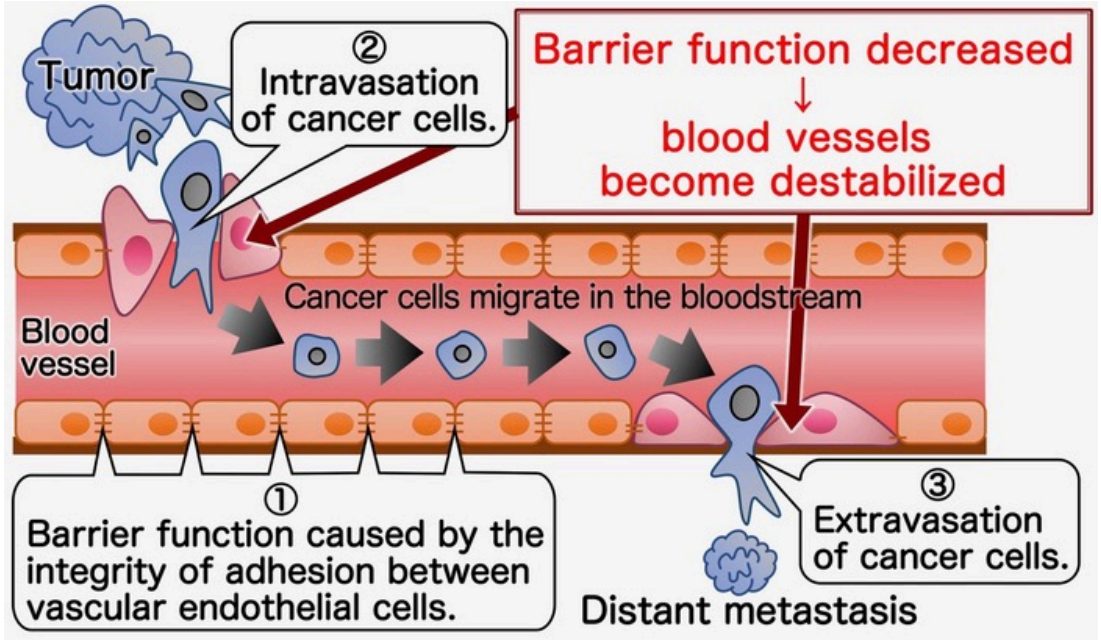
https://www.eurekalert.org/news-releases/970887

The How: How Can We Stop a Tumor from Metastasizing?



Legend: Light-blue - lymph vessels
Red - blood vessels

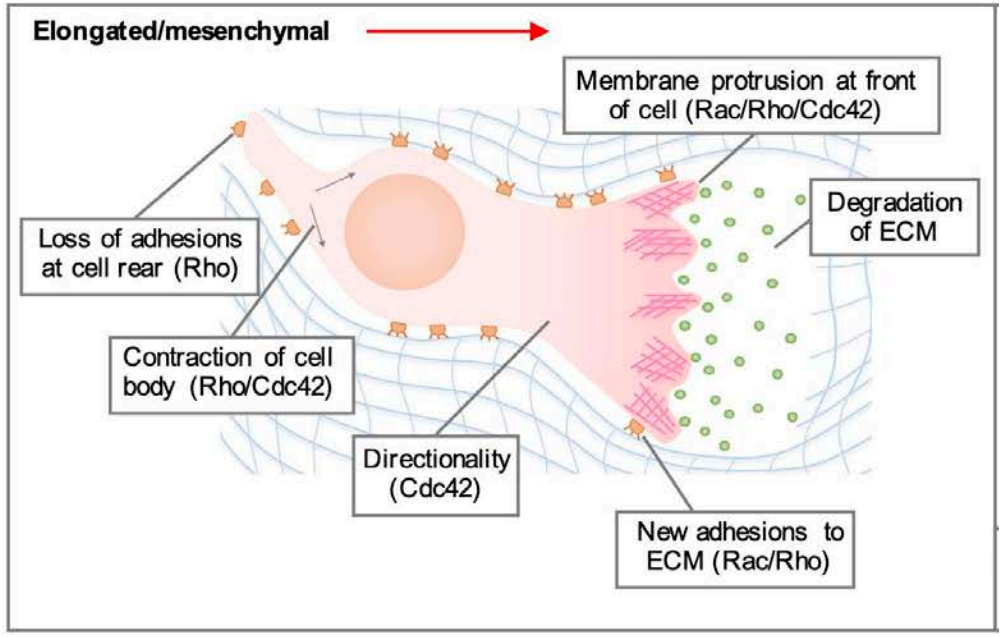
As tumors grow, they recruit blood vessels to feed them and lymph vessels that are a route of metastasis



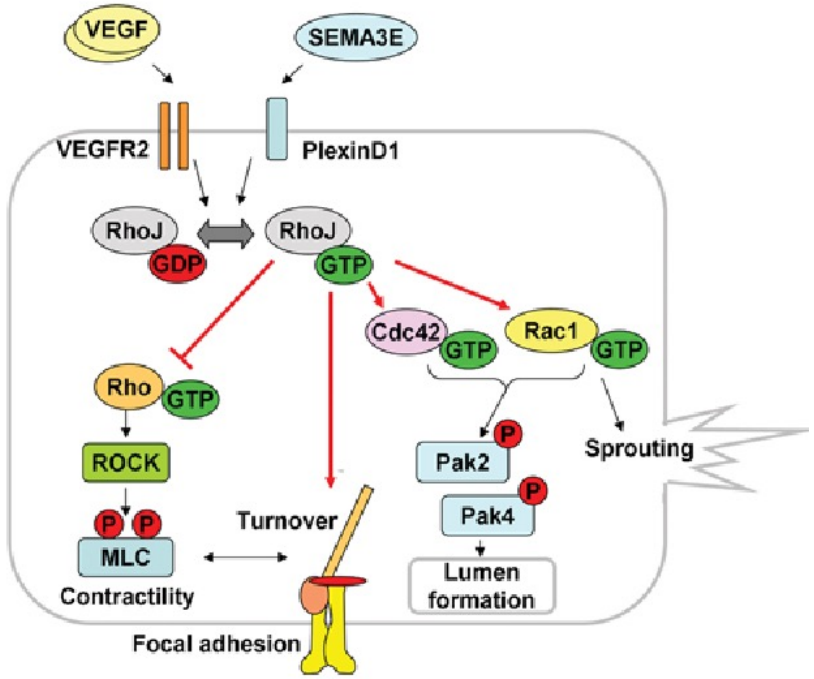
Tumors must be able to enter vessels and then leave them

If cancer cells can no longer recruit vessels, enter and leave them, they will no longer metastasize!

The Target: CDC42 GTPases Control Both Vessel Growth and Tumor Cell Migration



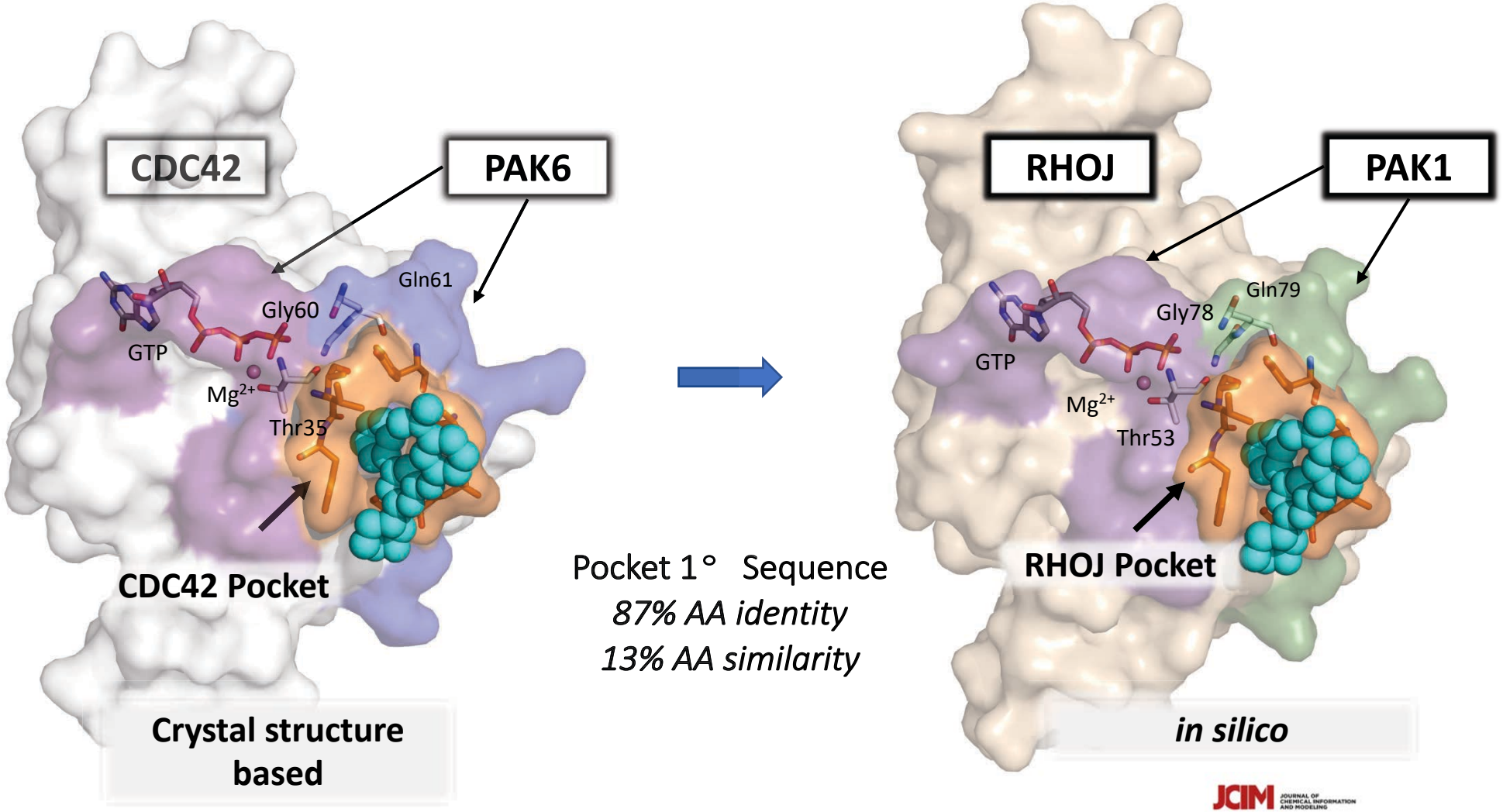
Clayton and Ridley Front. Cell Dev. Biol., 03 April 2020



Katarzyna B et al., 2011 Biochemical Society transactions

How Can We Selectively Target CDC42 GTPases?

The Approach: Target a Conserved Druggable Pocket at the Effector Interaction Surface of CDC42 GTPases



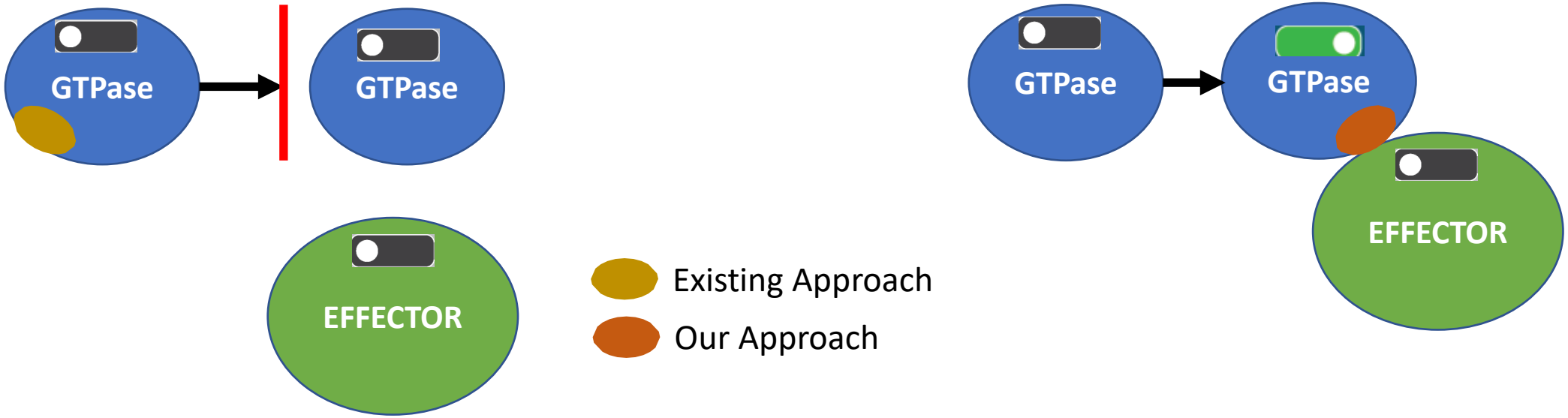
Courtesy De Vivo Laboratory

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING
pubs.acs.org/jcim
Article

Alchemical Free Energy Calculations to Investigate Protein–Protein Interactions: the Case of the CDC42/PAK1 Complex

Maria Antonietta La Serra, Pietro Vidossich, Isabella Acquistapace, Anand K. Ganesan, and Marco De Vivo*

What's Unique?: Our CDC42 Targeting Strategy



Target GTPase Activation

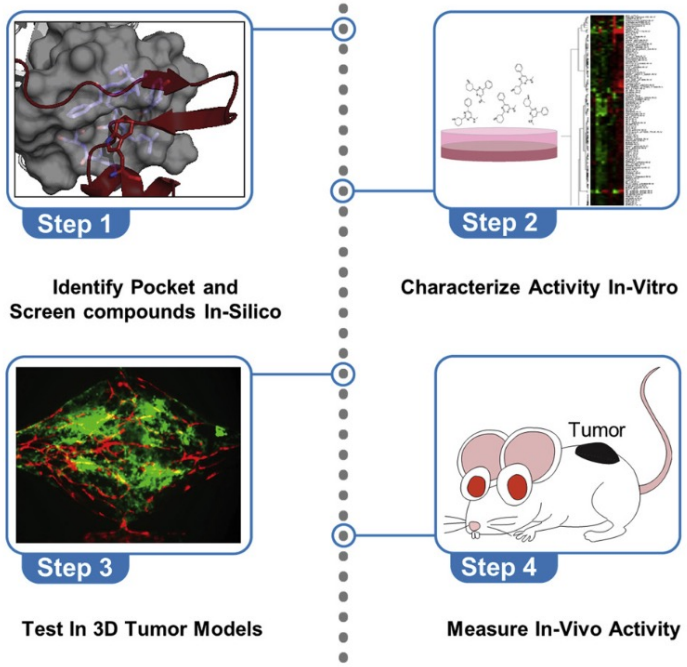
Existing RASG12C inhibitors, CDC42 inhibitors
Targets "off" conformation
Can be overcome by increasing rate of activation

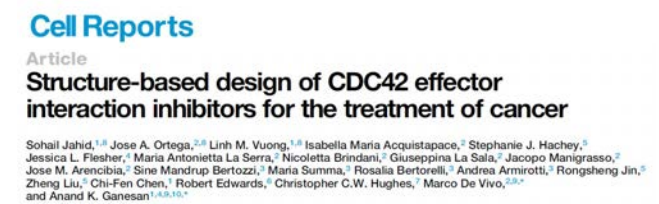
Target GTPase Function

Our GTPase targeting strategy
Targets "on" conformation
Cannot be overcome by increasing activation rate

By targeting the protein only when it is "on", we can avoid side effects seen when we target it when it is "off".

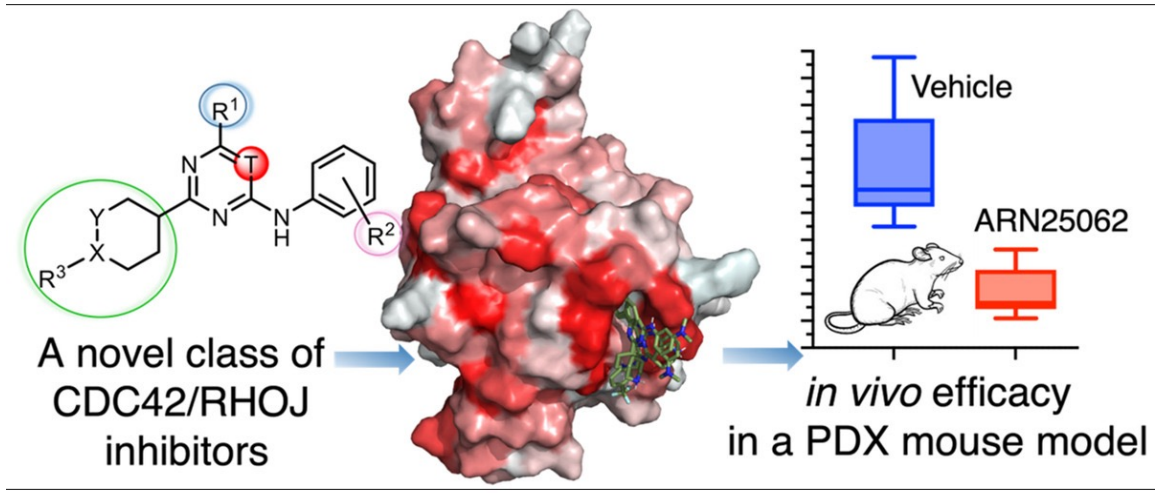
Drug Validation: Have Characterized the Molecule's Drug-Like Properties, Target Binding, and Activity




Cell Reports
Article
Structure-based design of CDC42 effector interaction inhibitors for the treatment of cancer

Sohail Jahid, Jose A. Ortega, Linh M. Vuong, Isabella Maria Acquistapace, Stephanie J. Hachey, Jessica L. Flesher, Maria Antonietta La Serra, Nicoletta Brindani, Giuseppina La Sala, Jacopo Manigrasso, Jose M. Arencibia, Sine Mandrup Bertozzi, Maria Summa, Rosalia Bertorelli, Andrea Armirotti, Rongsheng Jin, Zheng Liu, Chi-Fen Chen, Robert Edwards, Christopher C.W. Hughes, Marco De Vivo, and Anand K. Ganesan

Discovered new class of CDC42 Inhibitors with in vivo efficacy, Drug Lead ARN22089

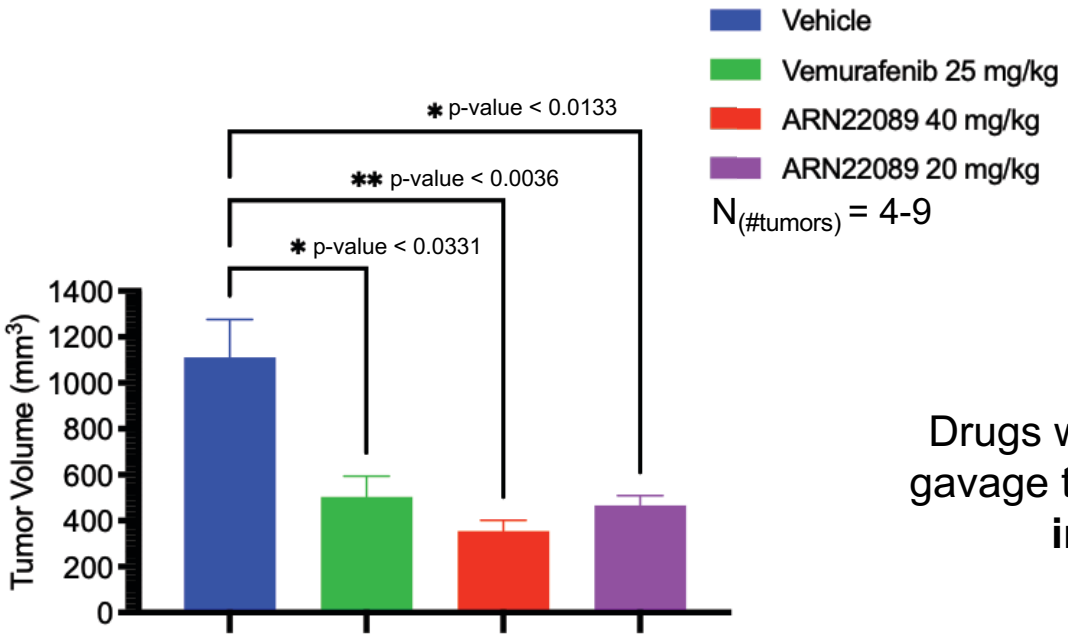



Journal of Medicinal Chemistry
pubs.acs.org/jmc
Article
Design, Synthesis, *In Vitro* and *In Vivo* Characterization of CDC42 GTPase Interaction Inhibitors for the Treatment of Cancer

Nicoletta Brindani, Linh M. Vuong, Isabella Maria Acquistapace, Maria Antonietta La Serra, José Antonio Ortega, Marina Veronesi, Sine Mandrup Bertozzi, Maria Summa, Stefania Girotto, Rosalia Bertorelli, Andrea Armirotti, Anand K. Ganesan, and Marco De Vivo

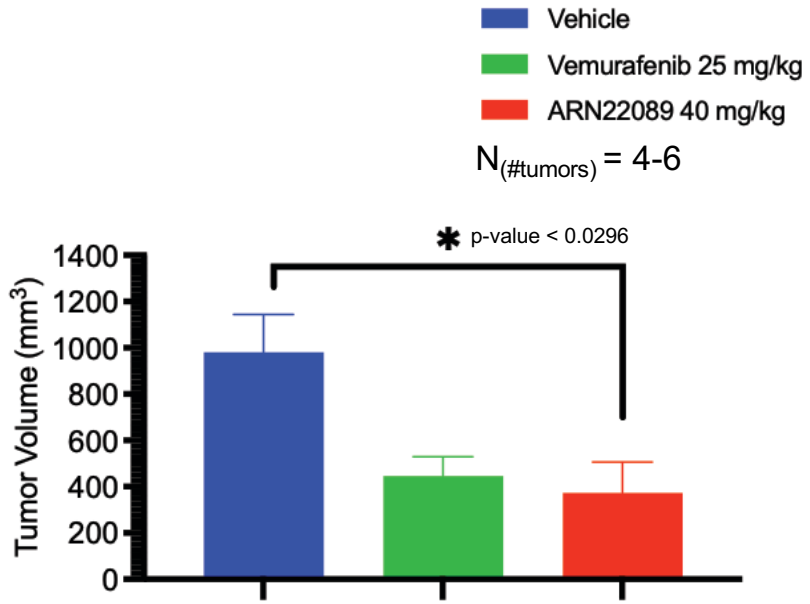
Detailed SAR, further *in vivo* validation Drug Backup ARN25062

Activity: Has Broad *in vitro* Activity and *in vivo* Activity



Human Melanoma PDX

Drugs were administered via gavage twice daily for 2 weeks
in vivo activity

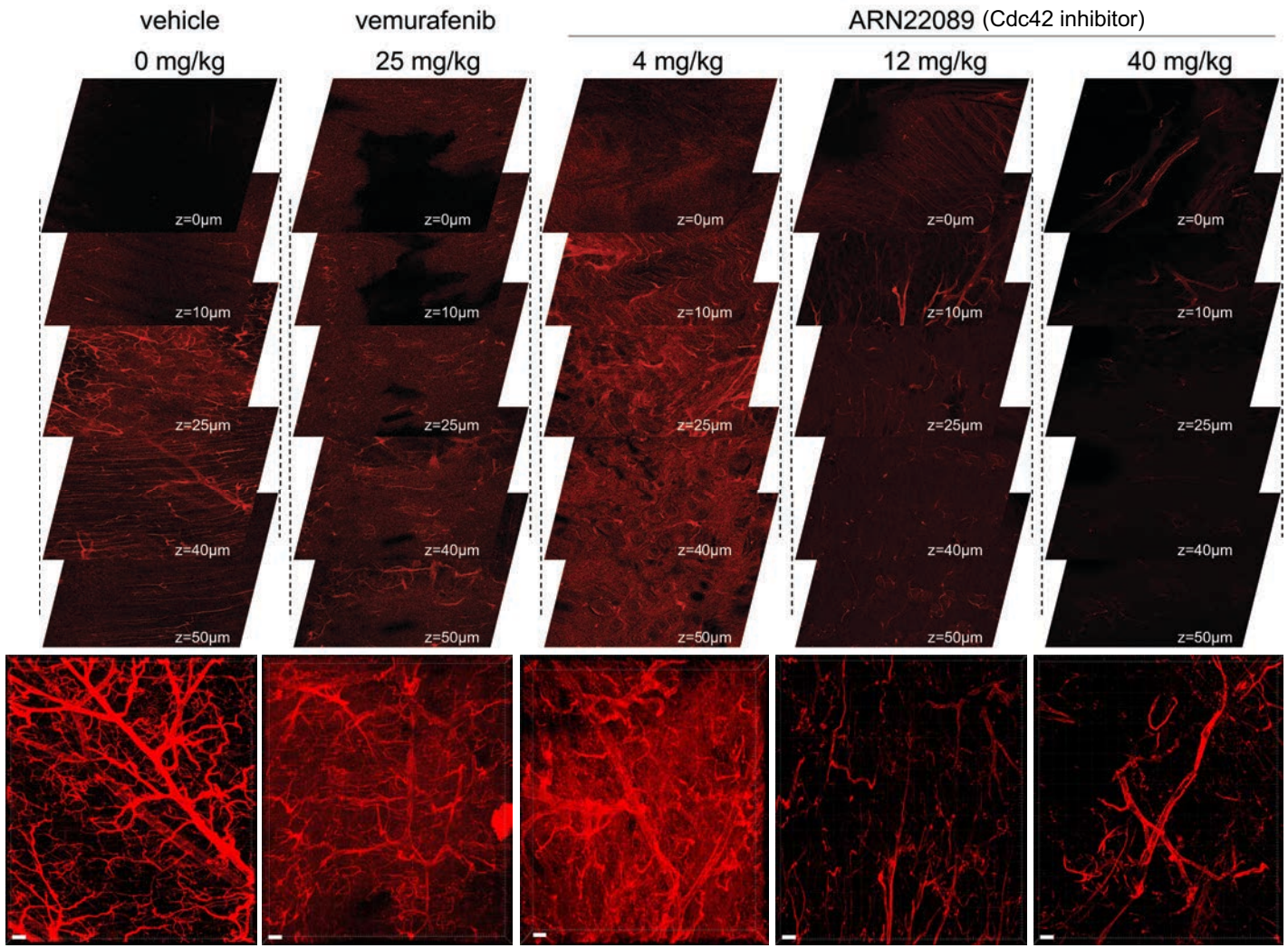


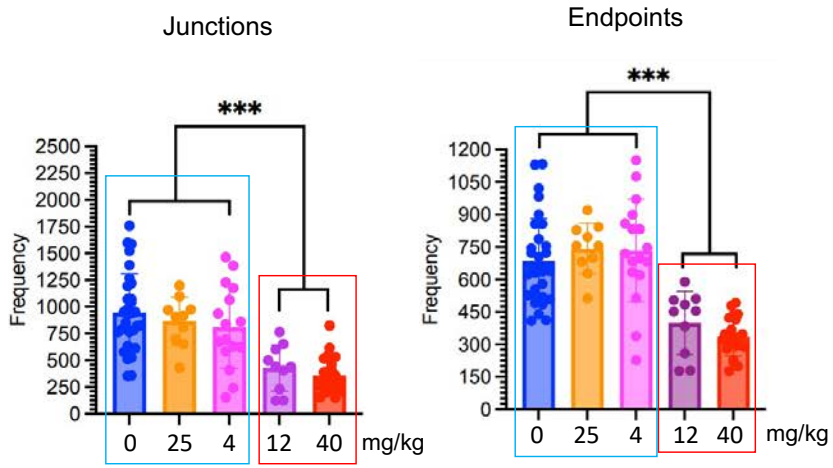
Melanoma YUMM1.7 Line
Immunotherapy resistant

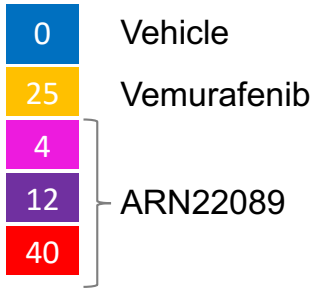
***In vitro* activity against 55/100 cell lines tested**

Vuong et al., in preparation

in vivo Activity: Blocks the Formation of Skin Vessels



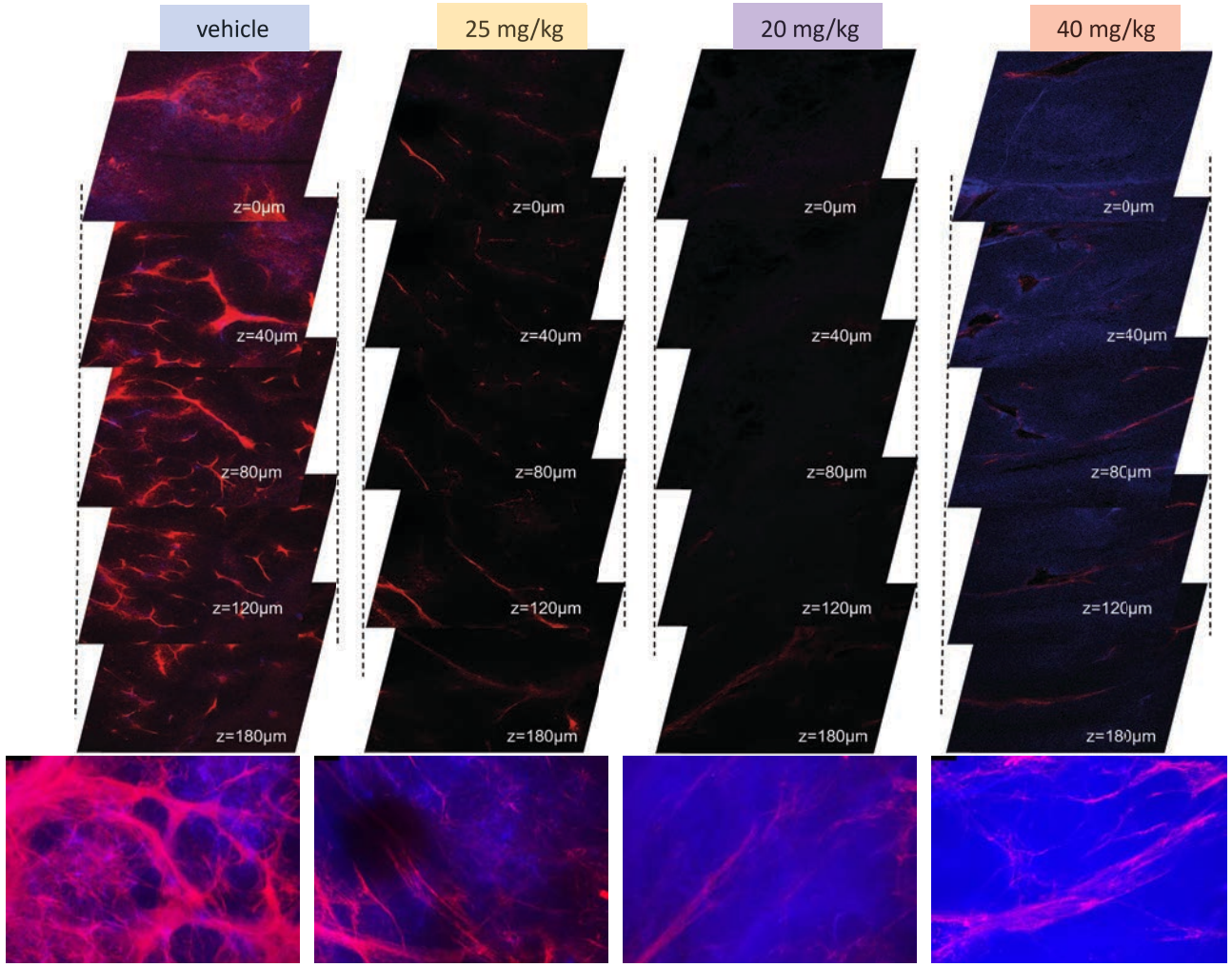


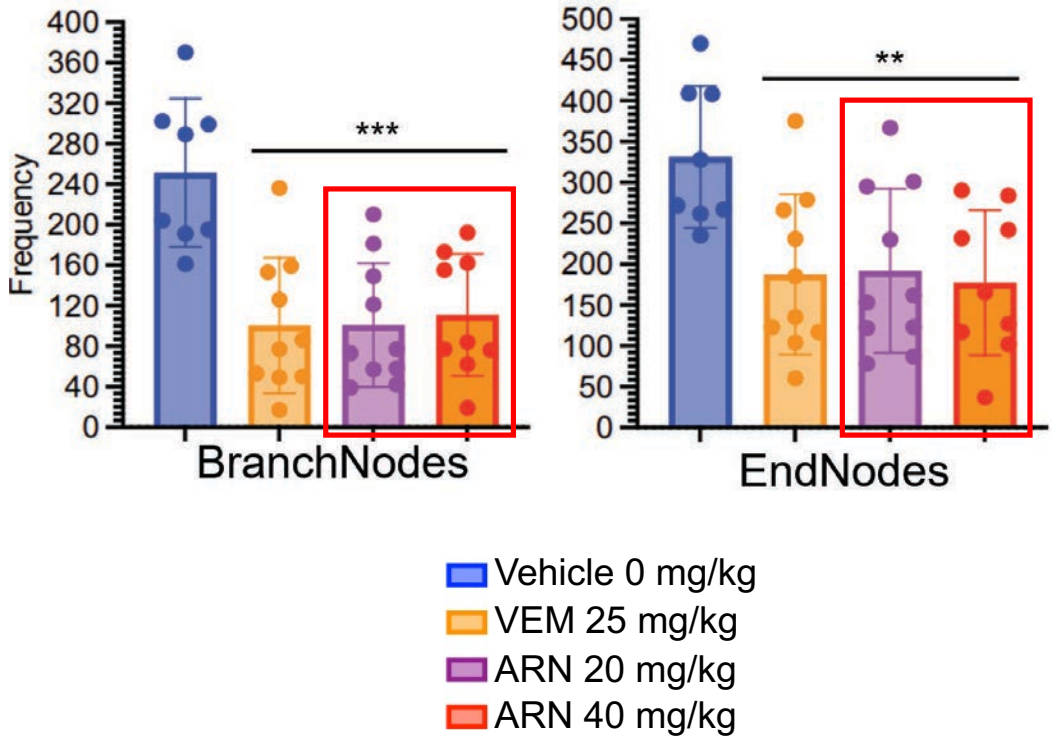


No effect on brain, limited effect on colon- **Skin specific vascular disruptor?**

Vuong et al., in preparation

in vivo **Activity:** Blocks Vessel Formation in Tumors *in vivo*





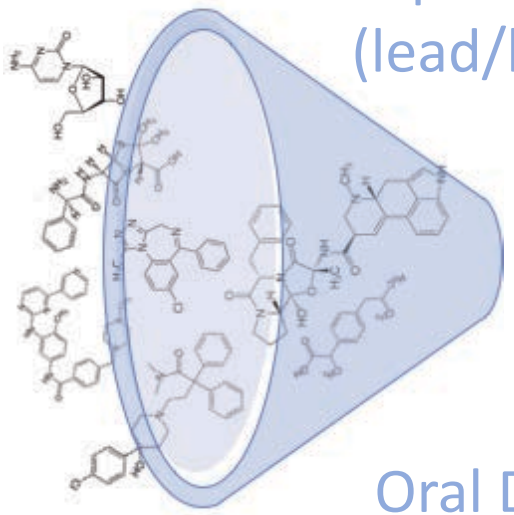
Vuong et al., in preparation

SUMMARY OF RESULTS AND WORK IN PROGRESS

- Key Advance
  - A new and effective strategy to target GTPase effector interfaces with small molecules
  - One drug candidate and a backup, validated *in vivo*, with drug like properties
  - Novel mechanism of action- Inhibits vessels (both blood and lymph) and cell growth, making it unique amongst existing therapies
  - Potent effects on skin, may be a topical for skin cancer treatment
- Publications
  - Three publications- one describing the lead, one reports multiple backup/follow-up compounds, and another describing an advanced computational method to target other GTPases. Two drugs with *in vivo* activity for further development.
- Intellectual Property
  - Global, exclusive rights to CDC42i and related compounds
  - US and EU patents granted, second for a new class submitted
- Scientific Work in Progress
  - Characterization of effect on angiogenesis in skin *in vivo* (in preparation)
  - Examination of efficacy in the context of kinase inhibitor resistance (Ganesan lab)
  - New IP and Chemical Series (de Vivo Lab)
  - Expanding the drug development pipeline to develop new RhoA inhibitors (De Vivo Lab)

One Class of Drugs with Two Cancer Applications

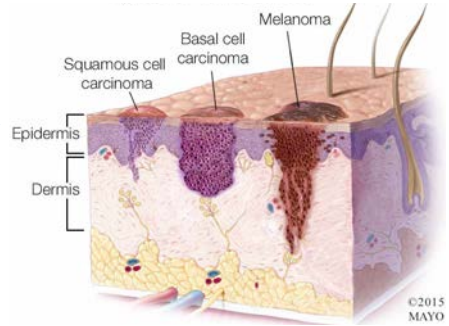
Drug Selection	Formulation Optimization	Pharm/Tox/GLP Efficacy	Disease Indications



Topical Drug
(lead/backup)

Topical Formulations

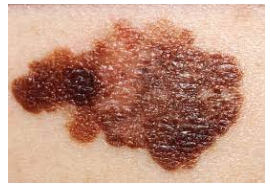
Topical Pharm/Tox
GLP formulation synthesis
Efficacy testing
in Skin Cancer Models



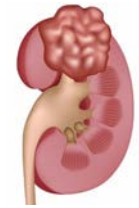
Oral Drug
(lead/backup)

Oral Salt

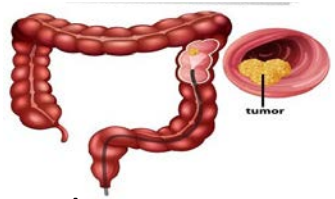
Oral Pharm/Tox
GLP synthesis
Efficacy in testing in
other Tumor Models



Melanoma

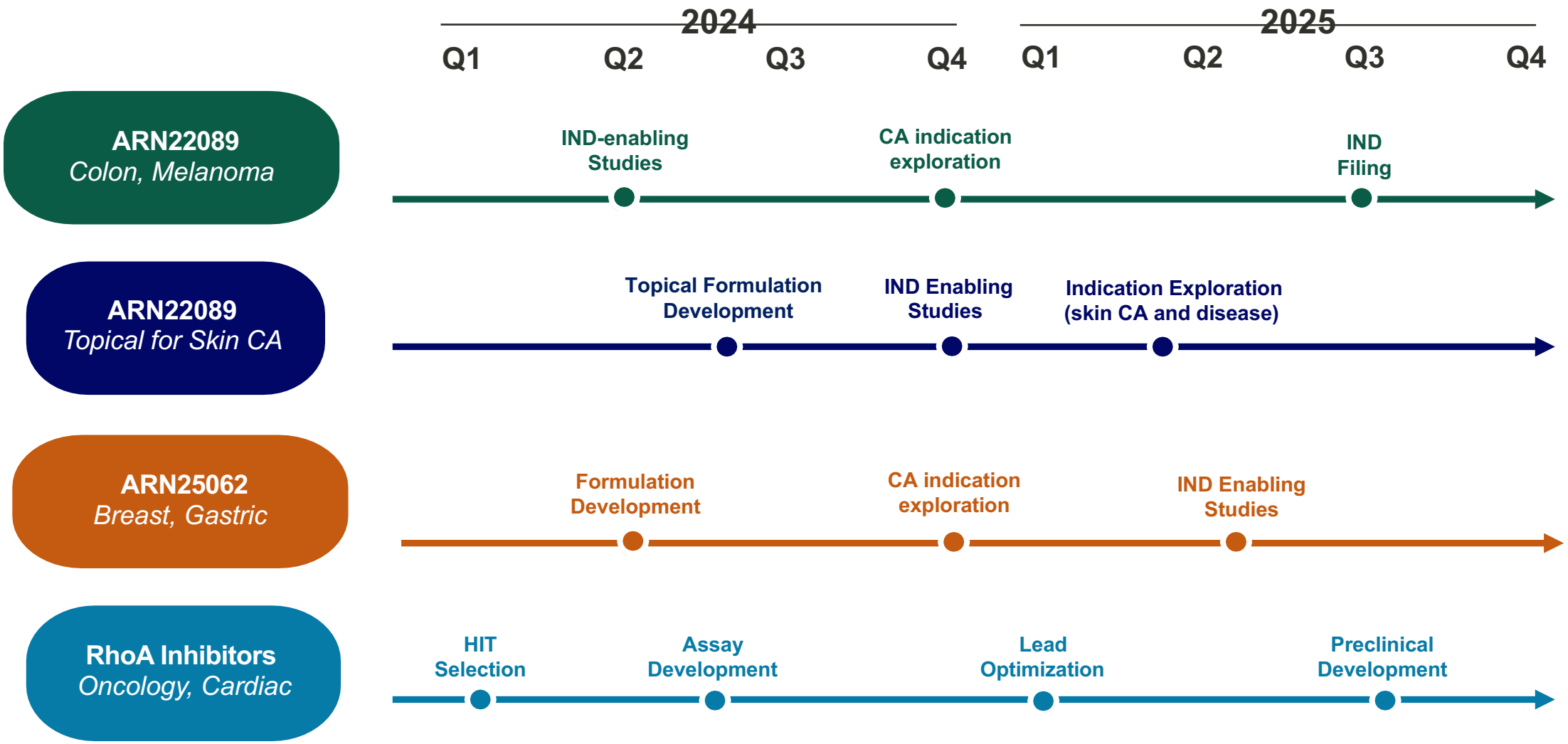


Renal Cell CA



Colon CA

Our Drug Development Pipeline



FUNDING

We look for a SEED or SERIES A for 10 M for:

- Additional formulation development (oral and topical)
- Pharmacology/Toxicology for the two routes (~7M up to IND/CTA filing)
- Efficacy testing in different indications (multiple cancer PDXs and skin CA (~2M))
- Progress back-up/follow-up compounds and strengthen/diversify our pipeline (~1M)
- Specific focus on lymphatics to prevent metastasis

In addition:

- Opportunities for additional targets and new compounds (new IP) targeting other GTPases

STRONG SYNERGISTIC SCIENTIFIC TEAM

Marco De Vivo, PhD

Computational Chemistry
Medicinal Chemistry
MOA Testing

Anand Ganesan, MD, PhD

Cancer Biology
Skin Biology
Research Translation

Each laboratory has an independent team of scientists working on the project