Targeting Hippo Signaling

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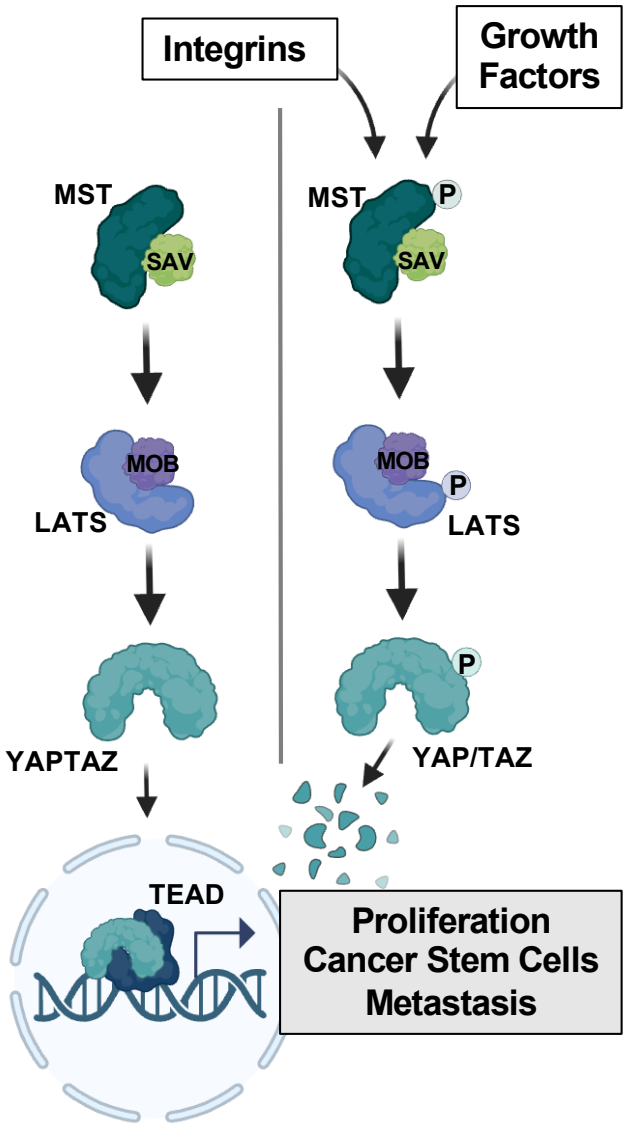
Targeting of Hippo Signaling



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Primary Tumors

- Translocation-Driven

Epithelioid hemangioendothelioma (EHE)

TAZ-CAMTA1

- NF2 Dependent Cancers
- Mesothelioma
- Sarcomas
- Subsets of Breast, GI, Lung

Drug Resistance

- EGFR inhibitors
- KRAS inhibitors
- Cisplatin, gemcitabine, docetaxel
- Imatinib

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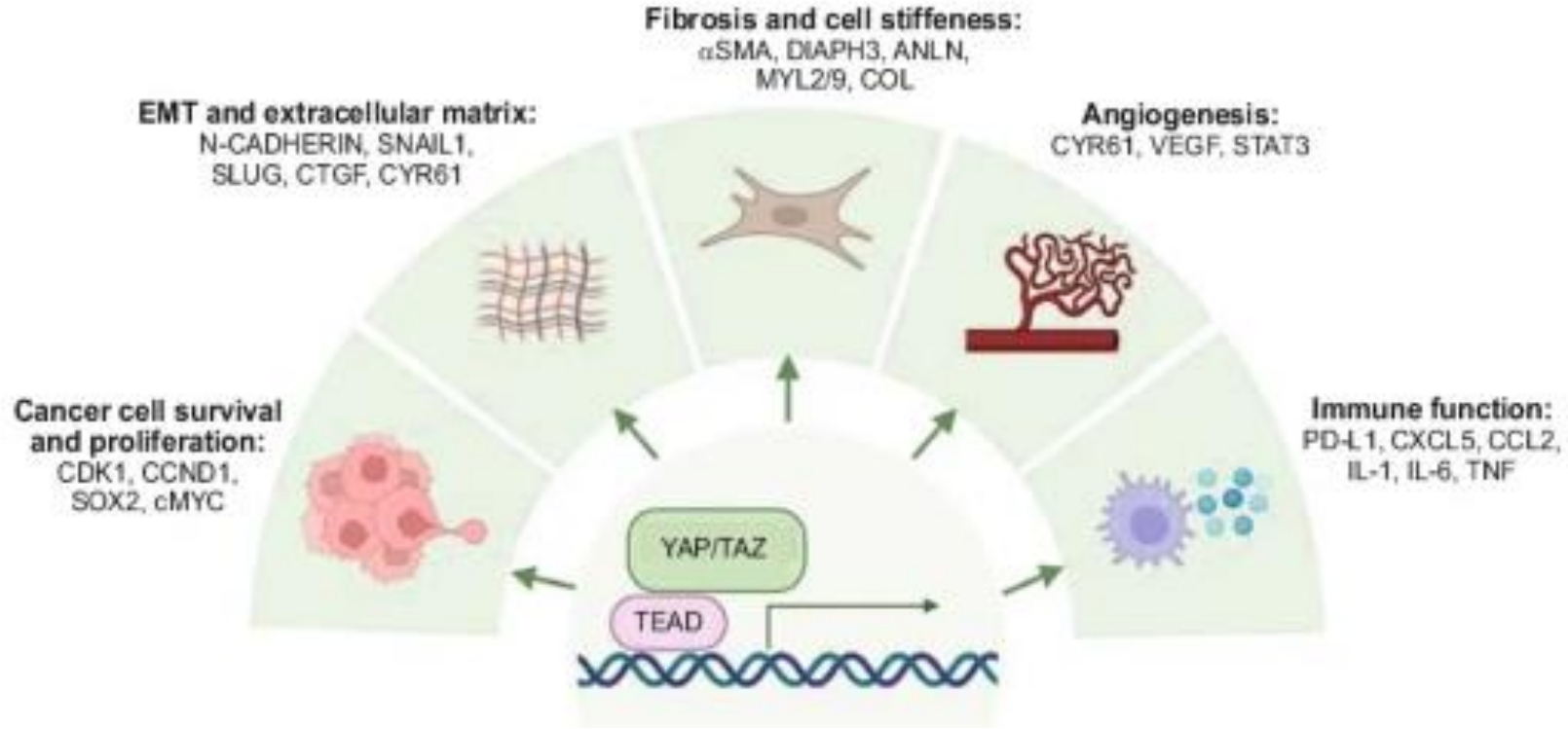
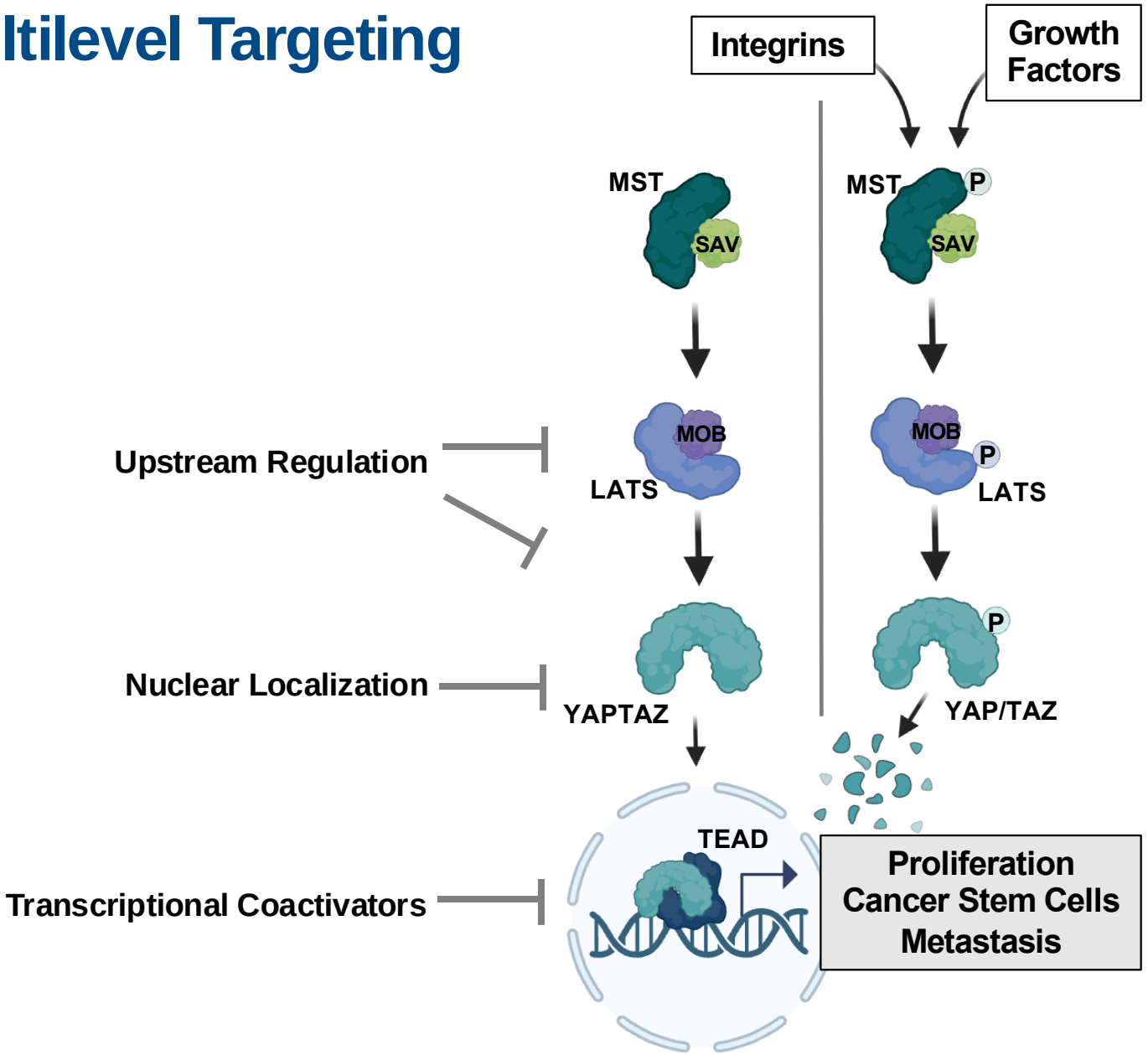
Hippo Signaling



Baroja et al. Nature Communications, 2024

Multilevel Targeting



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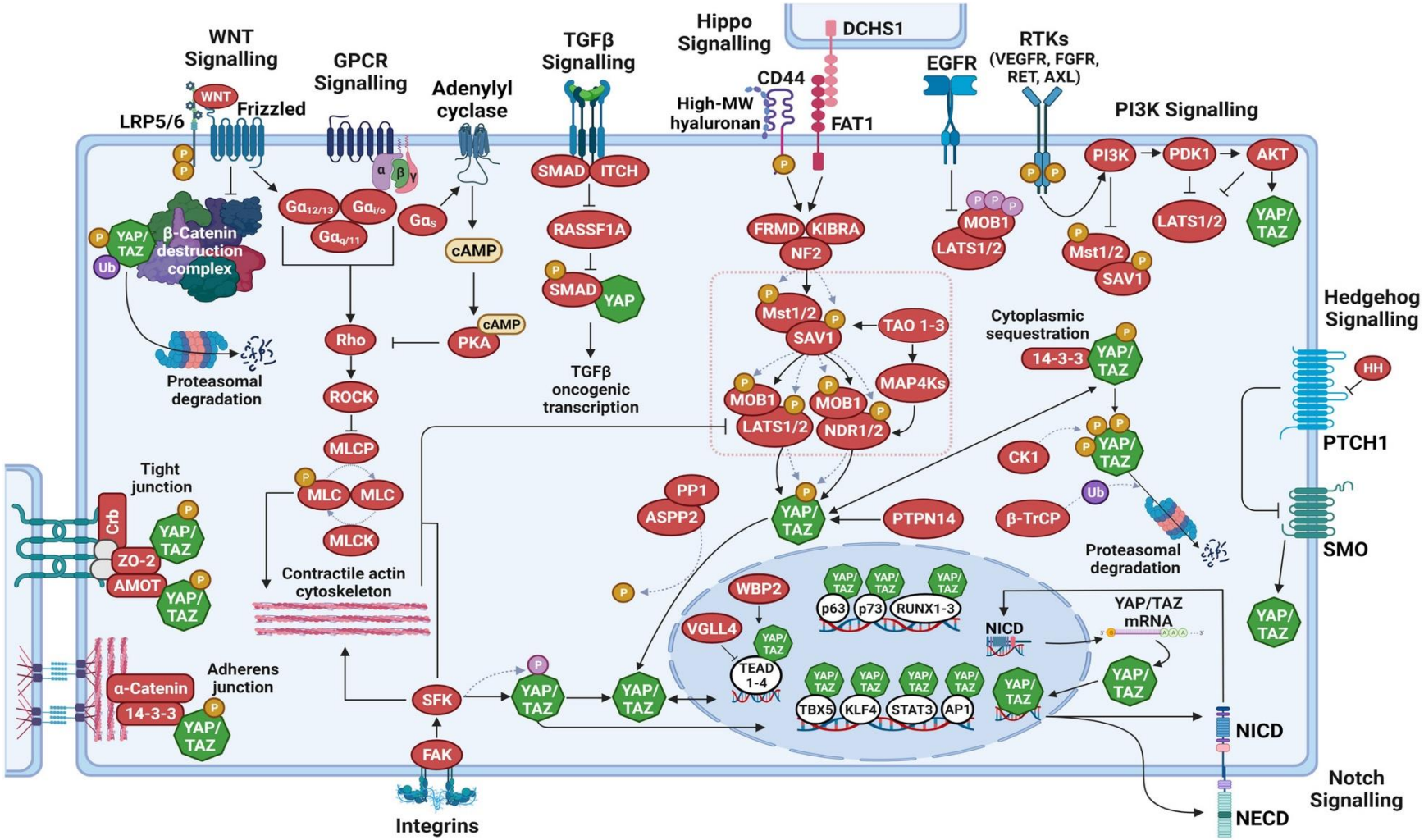
Upstream Regulation
Antisense RNA (NCT04659096)

Collota et al. Frontiers Pharmacology, 2023

Nuclear Localization
Tyrosine Kinase Inhibitors



Dasatinib
Pazopanib

Howard et al. Experimental Dermatology 2022

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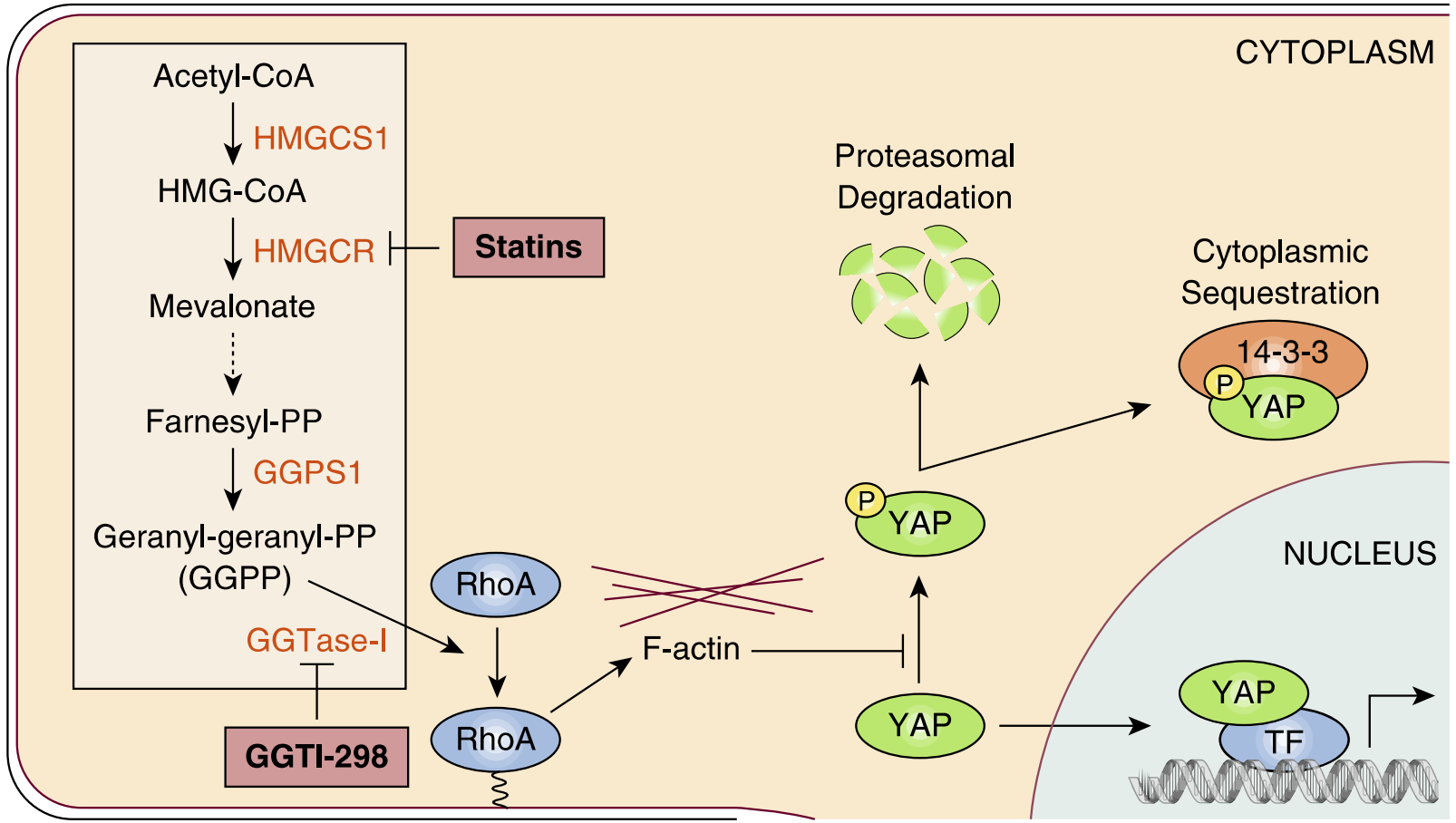
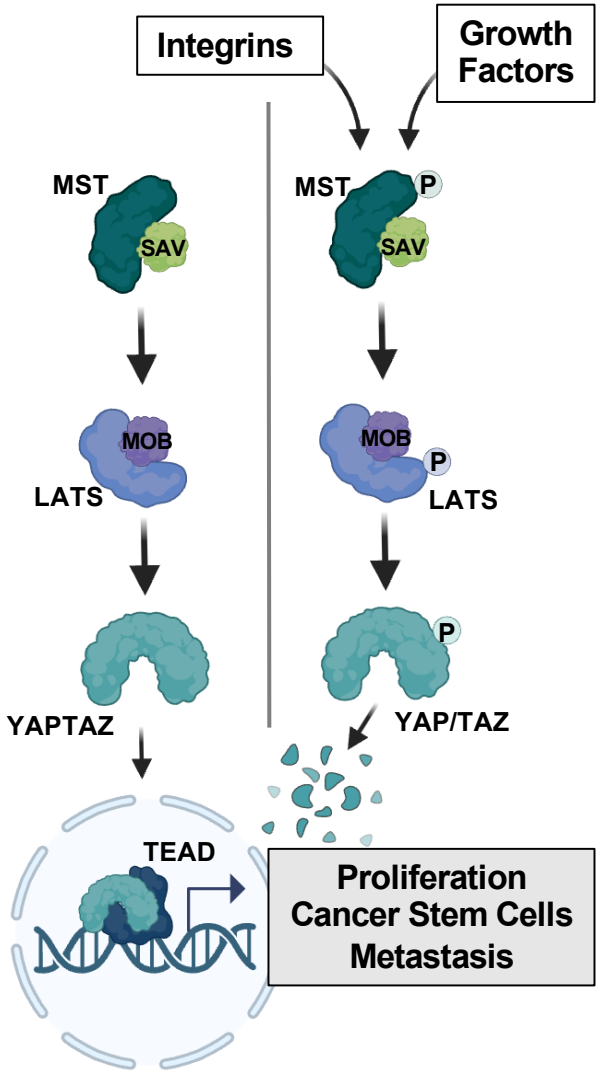
Nuclear Localization
Statins



Santos et al. 2020

Transcriptional Coactivators



Basis of Hippo Targeting

- YAP/TAZ do not have DNA binding domains and instead rely on transcriptional coactivators
- TEAD proteins are the major downstream YAP coactivators

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YAP-TEAD Inhibitors
NCT05228015 and NCT06251310 ongoing

First-in-class, first-in-human phase 1 trial of VT3989, an inhibitor of yes-associated protein (YAP)/transcriptional enhancer activator domain (TEAD), in patients (pts) with advanced solid tumors enriched for malignant mesothelioma and other tumors with neurofibromatosis 2 (NF2) mutations
YAP et al. AACR 2023

- Enrolled 67 pts (29 with MM). Median prior therapies 3 (range 0–8)

- Most common TRAEs: proteinuria, albuminuria and peripheral edema. 7 G3 TRAEs (fatigue, ↑ALT & AST, dehydration, dyspnea, hypotension, peripheral edema) and 1 G4 TRAE (cardiomyopathy)

- Results: 6 refractory MM achieved RECIST v1.1 PRs. 3 PRs in MM pts are ongoing up to 18+ months. Clinical benefit response rate (PR + SD >8 weeks, per protocol) in MM pts is 57%

Potential side effects

Nephrotoxicity

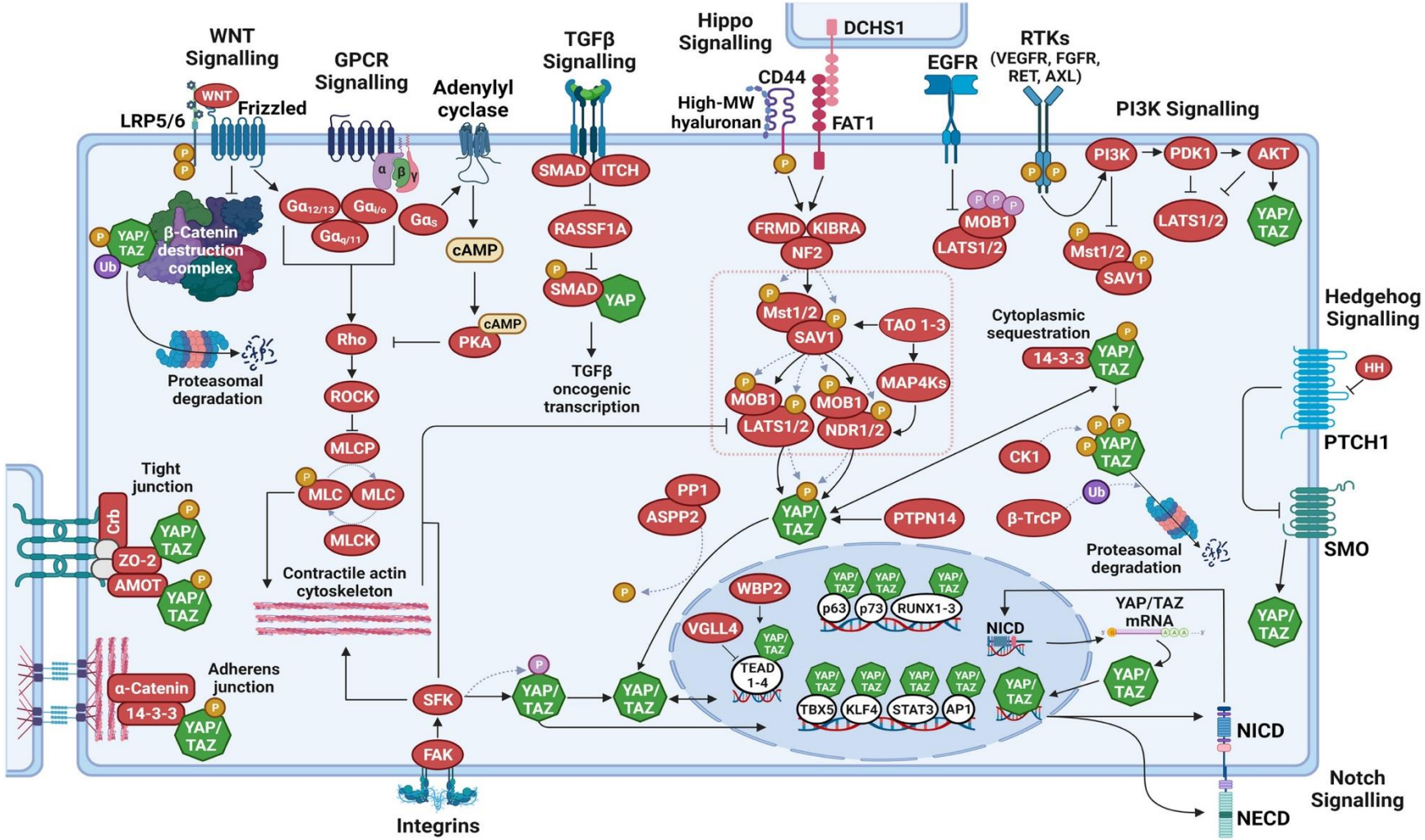
- Predicted from in vivo models
- Hippo is required for podocyte maintenance
- Loss of YAP from in vivo models led to progressive renal failure

Immunosuppression

- Immune regulatory roles

Wound Healing/Regeneration

Resistance Mechanisms



Howard et al. Experimental Dermatology 2022

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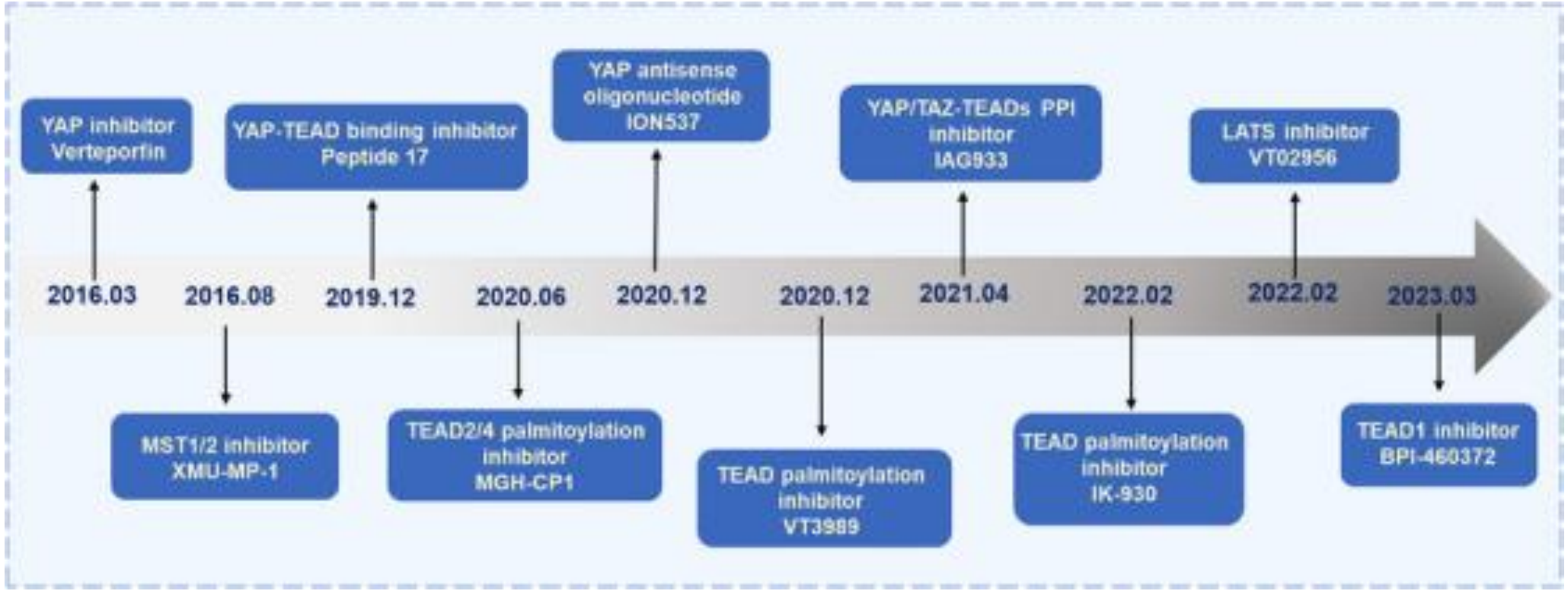
Hippo Targeting



Lv et al. 2023

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Conclusions

- Hippo signaling is critical for a subset of cancers (development, growth, metastasis, drug resistance): **NF2 mutated tumors, those with a translocation, malignant mesothelioma**
- Current methods of targeting the Hippo pathway focus on disrupting the **YAP/TAZ-TEAD** interaction, trials are ongoing
- Anticipated side effects include **nephrotoxicity**, immunosuppression and impaired wound healing
- One mechanism of resistance is through increased MAPK signaling which may create a basis for **combination therapies**

Lv et al. 2023