AACR 2021

Transformation in Cancer Treatment – Destroy vs. Inhibit?

The field of protein degraders is booming with innovation and intense pipeline activity, largely in preclinical development. Unlike inhibition approaches where the protein function can be restored after dissociation of the 'inhibitor', protein degraders destroy the target itself, and thus nullify the activity. Small molecules can induce selective degradation of the target protein of interest (POI) by adding a tag that is recognized by the degradation machinery.

This space is attractive due to:

- its potential to target 'undruggable proteins'
- the broad-spectrum activity, including resistant variants
- rapid action that should prevent emergence of resistant clones

As nearly one-fourth of all the protein degraders in development are likely to enter clinical development in the next year, questions remain about their ability to be differentiated.

Biotechs developing targeted protein degraders presented preclinical data at AACR 2021, primarily related to testing or validating their hypothesis of the level of differentiation of their 'targeted protein degraders'.

SmartAnalyst summarizes select AACR 2021 highlights on 'differentiated' approaches involving:

A Reversal of Drug Resistance

Resistant prostate cancer emerges rapidly with anti-deprivation therapies (ADT) and continues to be a persisting unmet need; resistant mechanisms may include intra-tumoral androgen synthesis and AR expression amplification/splice variants, even in the presence of ADT.

Arvinas is developing an AR targeting PROTAC, AR-110, which is currently in an early phase trial targeting heavily pre-treated mCRPC to reverse resistance to ADTs; preclinical validation of its expected differentiation vs. 2nd gen ADT (enzalutamide) was presented:

- Potent and selective degradation of AR in AR resistant (AR-V7 splice variant and TMPRSS2-ERG gene fusion+) prostate cancer cells
  - ➢ 85% degradation lasting 8 hours
- Demonstrated similar PSA reduction as enzalutamide but at *lower doses* in enzalutamide-sensitive models
- Significant tumor growth inhibition in both enzalutamide primary and secondary resistant tumor models

Key Question:

- Will the first in-class AR PROTAC, AR-110 have sustainable differentiation vs. other emerging in-class agents?

B Elusive 'Druggable' Targets

Selective suppression of SMARCA2 activity has been proposed as a therapeutic concept for SMARCA4 mutated cancers (dependent on SMARCA2 for survival) that contributes to ~10% of certain cancers.

- Intervention of SMARCA ATPase is known to be a better therapeutic strategy than the SMARCA bromodomain, given the cancer dependency; hence, SMARCA degradation is a novel therapeutic approach

Prelude Therapeutic's SMARCA2 selective degraders validated the following in preclinical studies –

- Synthetic lethality induced in SMARCA4 deleted cancer cells
- Formation of binary/ternary complexes w/ SMARCA2 and SMARCA4
- Selective degradation of SMARCA2 vs. SMARCA4
- Selective inhibition of SMARCA4-del-NSCLC cancer cells and PD lung cancer cells, mediated by downregulation of cell cycle & proliferation gene signatures

Key Question:

- Will orally available, selective SMARCA2 degraders avoid potential toxicity issues resulting from degradation of SMARCA4?

C Obliteration of the Need for an E3 Ligase

Recruiting specific E3 ligases (orchestrate ubiquitinylation of target proteins for degradation) translates into a dependency on a relatively narrow set of chemical moieties that bind those ligases, leading to challenges in target choices, and drug design. Some companies developing protein degraders are trying to bypass the need for an E3 ligase to induce chemical induced proximity for protein degradation.

Ranok Therapeutic's chaperone-mediated protein degradation (CHAMP) induces proximity between a target protein and chaperone complexes, thereby degrading the target via the ubiquitin proteosome system (UPS); it is pursuing a BRD4-CHAMP that preferentially degrades BRD4 vs. other HSP90-regulated proteins with evidence presented on the following:

- Potent in vivo/in vitro degradation of BRD4
  - ➢ 90% degradation up to 72h in vivo AML model
  - ➢ Superior in vivo efficacy vs. MK-8628, a pan-BETi
  - ➢ Prolonged PK in tumors vs. normal tissues in vivo
- CHAMP technology can be used to degrade proteins not regulated by HSP90, eg. KRASG12C

Key Question:

- How will evasion of emerging resistance mutations and potentially better safety by CHAMP technology position it versus other approaches?

The expanding research and development of new protein degraders and degrader tools make it worth believing that they will become another important modality, as well as herald a new era of 'emerging' innovation.

References:

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2. Zeng S. et al. European Journal of Medicinal Chemistry 210 (2021) 112981
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4. Snyder L. B. et al. AACR 2021, Abs#43/ Arvinas
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6. Company websites/News Releases

SmartAnalyst is helping clients interpret the data presented at AACR 2021, to assess the impact on their drug development programs and future asset and portfolio strategies. **For more information contact us**

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