Discovery and development of allosteric inhibitors of SHP2

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AACR, Chemistry to the Clinic: Lead Optimization Case Studies in Cancer Drug Discovery

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Disclaimer

employee & stockholder of Revolution Medicines
SHP2 - Shared Node that Regulates RAS Signaling Pathway

Multiple Receptor Tyrosine Kinases (RTKs)

- PI3K
- PTEN
- AKT
- TSC1/2
- mTORC1
- 4EBP1
- S6K
- Oncogenes

RAS(ON) → RAF → MEK → ERK → Growth, Survival

RAS(OFF) → GDP

SOS1

NF1

Oncogenic mutants sensitive to SHP2 inhibitor

- SHP2

Drugging SHP2 Requires Novel Approaches

Auto-inhibition and Activation of SHP2

Closed, inactive SHP2

Allosteric inhibitor

Y-\(\circ\)

Open, active SHP2

Drugging SHP2 Requires Novel Approaches

RevMed chemical series exploits natural intra-molecular allosteric regulation of SHP2


Auto-inhibitory (SH2) domains

Phosphatase catalytic domain
Allosteric Inhibitors: From Tools to Lead Discovery
Structure and Physicochemical Property Guided Exploration

CH$_3$ occupies a pocket with partially hydrophobic character

<table>
<thead>
<tr>
<th>Compound</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHP2 IC$_{50}$ (nM)</td>
<td>104</td>
<td>39</td>
</tr>
<tr>
<td>SHP1 IC$_{50}$ (µM)</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>PC9 pERK IC$_{50}$ (nM)</td>
<td>2000</td>
<td>452</td>
</tr>
<tr>
<td>LE/LLE</td>
<td>0.4/3.5</td>
<td>0.4/3.3</td>
</tr>
</tbody>
</table>

Druglike chemical equity with promising lead-like profile and scope for optimization
Structure-Guided Pyrazine Ring Modifications Led to Significant Potency Boost

Para-substitutions modulate biochemical and cell potency; opportunity to improve physicochemical properties.

<table>
<thead>
<tr>
<th>Tool Compound 2</th>
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</thead>
<tbody>
<tr>
<td>SHP2 IC₅₀ (nM)</td>
<td>39</td>
</tr>
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<td>PC9 pERK IC₅₀ (nM)</td>
<td>452</td>
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<tr>
<td>LE/LLE</td>
<td>0.4/3.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound 3</th>
<th>Early SAR compound</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SHP2 IC₅₀ (nM)</td>
<td>624</td>
<td></td>
</tr>
<tr>
<td>PC9 pERK IC₅₀ (nM)</td>
<td>4220</td>
<td></td>
</tr>
<tr>
<td>LE/LLE</td>
<td>0.29/1.9</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound 4</th>
<th>Early SAR compound</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>SHP2 IC₅₀ (nM)</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>PC9 pERK IC₅₀ (nM)</td>
<td>431</td>
<td></td>
</tr>
<tr>
<td>LE/LLE</td>
<td>0.36/4</td>
<td></td>
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<thead>
<tr>
<th>Compound 5</th>
<th>Early SAR compound</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SHP2 IC₅₀ (nM)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>PC9 pERK IC₅₀ (nM)</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>LE/LLE</td>
<td>0.40/4.6</td>
<td></td>
</tr>
</tbody>
</table>
Significant Optimization Efforts Led to the Identification of Rodent Tool Compound RMC-4550

- High solubility, permeability, no efflux
- Clean CYP450 profile, excellent in vivo combination partner

Key Interactions of RMC-4550 with SHP2

Auto-inhibitory (SH2) domains

Phosphatase catalytic domain
RMC-4550 is a Potent, Non-competitive Inhibitor of Human SHP2

- Biochemical and biophysical characteristics are consistent with an allosteric mode of action

<table>
<thead>
<tr>
<th></th>
<th>IC$_{50}$ (nM)</th>
<th>$K_i$ (nM)</th>
<th>$k_{cat}$ (min$^{-1}$)</th>
<th>$K_m$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMC-4550</td>
<td>1.55</td>
<td>2.6</td>
<td>1100</td>
<td>170</td>
</tr>
</tbody>
</table>
RMC-4550 is a Potent Inhibitor of the RAS-MAPK Pathway in RTK-Driven Cancer Cell Lines in Vitro

- Potent RAS-MAPK pathway suppression (pERK)
- Inhibition of growth in RTK-driven lines
Significant Improvements Made in Lead Series Physicochemical Properties
RMC-4630: A Clinical Candidate with High Quality Drug-like Profile

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>SHP2 biochemical potency (IC&lt;sub&gt;50&lt;/sub&gt;, nM)</td>
<td>1.3</td>
</tr>
<tr>
<td>Cellular pERK potency (IC&lt;sub&gt;50&lt;/sub&gt;, nM) (NCI-H358)</td>
<td>20</td>
</tr>
<tr>
<td>Inhibition of cell proliferation (IC&lt;sub&gt;50&lt;/sub&gt;, nM) (NCI-H358)</td>
<td>32</td>
</tr>
<tr>
<td>Solubility (0.2% BSA pH 7.2, µM)</td>
<td>180</td>
</tr>
<tr>
<td>Permeability MDCK cells one way A-B (nm/s)</td>
<td>125</td>
</tr>
<tr>
<td>CYP450 inhibition/induction</td>
<td>None</td>
</tr>
<tr>
<td>Plasma protein binding % bound; mouse, rat, dog, human</td>
<td>65, 70, 60, 60</td>
</tr>
<tr>
<td>Oral bioavailability (m, r, d, m %)</td>
<td>(100, &gt;100, &gt;100, 73)</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt; 500</td>
</tr>
</tbody>
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- Potent and highly selective inhibitor of human SHP2
- High oral bioavailability with linear PK enables intermittent dosing strategy
- Toxicity profile ‘on target’: manageable and reversible
- Low DDI potential – enables combination strategy
RMC-4630 Exhibits Dose-Dependent Activity & PK/PD in the NCI-H358 KRAS\textsuperscript{G12C} NSCLC Xenograft Model

Anti-Tumor Activity

PK/PD Following Single Dose

End of Study Tumor Responses

\textbf{Anti-Tumor Activity}

- Control \( n = 10 \)
- RMC-4630 10 mg/kg po qd
- RMC-4630 30 mg/kg po qd

\( *p<0.05, **p<0.001, \) one-way ANOVA

\textbf{PK/PD Following Single Dose}

\textbf{End of Study Tumor Responses}

Time post dose \( 2h \quad 8h \quad 16h \quad 24h \)
Time post second dose (bid) \( 2h \quad 8h \)

\% Inhibition of \( \text{pERK/ERK} \)

\% change in tumor volume

\% inhibition of \( \text{pERK/ERK} \) relative to control

\( \text{EC}_{50} = 27 \text{ nM} \)
RMC-4630 + MEK Inhibitor Combination Drives Regressions in NF1\textsuperscript{LOF}, BRAF\textsuperscript{Class3}, KRAS\textsuperscript{Amp} and KRAS\textsuperscript{G12C} NSCLC Models
Intermittent Dosing of RMC-4630

**NCI-H358 CDX (KRAS\textsuperscript{G12C})**

### Anti-Tumor Activity

- Control \( n = 9 \)
- RMC-4630 10 mg/kg po qd
- RMC-4630 30 mg/kg po qd
- RMC-4630 120 mg/kg po q2d

***\( p < 0.001 \), one-way ANOVA

**MTD for daily dosing**

### Body Weight Loss

Dosing start

### End of Study Tumor Responses

- \( n = \text{number of regressions > 10\% at end of treatment} \)
- Each animal represented as a separate bar
**Broad Development Program for RMC-4630 Progressing Well**

**Monotherapy**
Dose escalation and schedule exploration (including expansion cohorts with molecularly-defined tumors)

**Combination therapy**
Molecularly-defined solid tumors

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<table>
<thead>
<tr>
<th>2019</th>
<th>2020</th>
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<tbody>
<tr>
<td><strong>RMC-4630-01</strong></td>
<td>RP2DS</td>
</tr>
</tbody>
</table>

*Daily and Intermittent* dosing schedules

**RMC-4630-02**

- **Roche** MEK
- **AMGEN** KRAS\(^{G12C}\) (OFF) **AMG 510**
- EGFR Inhibitor (osimertinib)
- PD-1 Inhibitor
- ERK inhibitor (IST)
RMC-4630 Monotherapy Shows Activity in Patients with KRAS Mutated NSCLC

* Confirmed PR  # Unconfirmed PR

Ou et al. AACR-IASCLC 2020
• RMC-4550 is a potent, selective and orally bioavailable SHP2 inhibitor, a high quality tool compound to study the role of SHP2 in tumour biology, both in vitro and in vivo

• SAR studies on RMC-4550 series enabled the discovery of our Clinical Candidate, RMC-4630

• RMC-4630 has ideal properties for clinical development, including a manageable and reversible safety/tolerability and linear PK profile, absence of drug-drug interactions and independent clinical activity against tumours with certain RAS pathway mutations, particularly NSCLC harboring KRAS\textsuperscript{G12C}

• RMC-4630 is currently in clinical testing as a monotherapy and in combination with MEK inhibitor, combinations with KRAS\textsuperscript{G12C} inhibitor, ERK inhibitor and anti-PD1 agent are underway
Acknowledgements

- Revolution Medicines Research and Development teams
- Sanofi team
- Bivona Lab, UCSF
- Investigators and Clinical Collaborators

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