Discovery of Novel Imidazolines and Imidazoles as Selective TAAR1 Partial Agonists for the Treatment of Psychiatric Disorders

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F. Hoffmann-La Roche AG, Basel, Switzerland
Biological Rationale

Trace amines are known for four decades

Trace Amines

- β-phenylethylamine (PEA)
- p-tyramine
- p-octopamine
- tryptamine

Biogenic Amines

- dopamine (DA)
- norepinephrine (NE)
- serotonin (5-HT)

- Structurally related to classical biogenic amine neurotransmitters (DA, NE, 5-HT)
- Co-localised & released with biogenic amines in same cells and vesicles
- Low concentrations in CNS, rapidly catabolized by monoamine oxidase (MAO)
- Dysregulation linked to psychiatric disorders such as schizophrenia & depression
Trace Amines

Metabolism

- **L-Phenylalanine** → AADC → β-Phenylethylamine → NMT → N-Methylphenylethylamine → MAOB → Phenylacetic acid
- **L-Tyrosine** → TH → AADC → p-Tyramine → PNMT → N-Methyltyramine → MAOA/B → p-Hydroxyphenylacetic acid
- **L-Tryptophan** → AADC → Tryptamine → PNMT → N-Methyltryptamine → MAOA/B → p-Hydroxymandelic acid
- **L-Tryptophan** → AADC → Tryptamine → PNMT → MAOA → Indoleacetic acid
Biological Rationale

*Trace Amine-Associated Receptors (TAARs)*

- First discovered in 2001 (Borowsky & Bunzow); characterised and classified at Roche in 2004
- **Trace amines** are endogenous ligands of TAAR1
- TAAR1 is expressed throughout the limbic and monoaminergic system in the brain


Biological Rationale

*Electrical activity of dopaminergic neurons*

The TAAR1 agonist downregulates dopaminergic neurotransmission in neurons from WT but not from KO mice.

**Working hypothesis** based on electrophysiology and behavioral effects of cmpds in rodents

- **TAAR1 is a negative modulator of dopaminergic neurotransmission**
- **TAAR1 full agonist** lowers DA if is too high (➔ **schizophrenia**)
- **TAAR1 partial agonist / antagonist** raises DA if too low (➔ **depression**)
- **TAAR1 partial agonist** might normalize DA if too low (➔ **bipolar disorder**)

Medicinal Chemistry Programme

**Aim: Discovery of selective TAAR1 agonists**

**Objectives:**
- Identify potent and selective TAAR1 agonists & partial agonists
- Drug-like series with suitable phys.-chem. and PK properties
- Use to probe behavioural pharmacology in animal models (POC)

**Challenges:**
- The natural ligands are not well suited as *in vivo* tool compounds due to their low metabolic stability (MAO substrates)
- Selectivity vs. biogenic amine targets may be difficult to achieve

**Strategy:**
Screening a subset of the Roche library to find suitable starting points and optimise these hits in a medicinal chemistry programme
HTS of Roche Golden Library

**Numbers**

52'757 cpds (Golden Library) → HTS

- Confirmation of primary hits and counter screen

  181 specific hits with EC_{50} < 10 \mu M (372 specific hits with EC_{50} < 50 \mu M)

- Similarity search → looking for clusters of parent molecules

2'672 cpds to be tested

- Selecting and eliminating (partly manual)

  191 new hits with EC_{50} < 10 \mu M; 78 with EC_{50} < 1 \mu M
TAAR1 Agonist Pharmacophore
Starting point for screening activities

Screening lead to identification of **2-benzylimidazolines** as drug-like TAAR1 ligands

Question: Can we find ligands that are **selective** vs. adrenergic receptor?
**Benzylimidazolines and Benzylimidazoles**  
*Structure Activity and Selectivity Relationship*

Preliminary SAR within 2-Benzylimidazole series showed promising selective versus adrenergic receptors when two substituents were added in ortho-position on the phenyl ring.

<table>
<thead>
<tr>
<th>R¹, R²</th>
<th>Kᵢ hTAAR1</th>
<th>Kᵢ hTAAR1/Kᵢ α²</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>400 nM</td>
<td>4.7</td>
</tr>
<tr>
<td>o,o'-diMe</td>
<td>36 nM</td>
<td>4.5</td>
</tr>
<tr>
<td>o,o'-diEt</td>
<td>24 nM</td>
<td>100</td>
</tr>
<tr>
<td>o,o'-diPr</td>
<td>630 nM</td>
<td>14</td>
</tr>
</tbody>
</table>

**Restricted SAR**  
No selectivity vs. α²A

![Chemical Structures](image)
2-Benzyl-imidazoles

Structure Activity and Selectivity Relationship

R: Me ~ Et > cBu ~ iPr > nPr, Ph, OH

R ≠ H: 0 or 1 o-substituent allowed:
- o: H, F, Br, Cl, OMe, CF₃, Et
- m: Br, Cl, F, OMe, CF₃

disubstituted derivatives:
- o,m': Cl/Cl, F/F
- o,m: F/F, Me/Me

R = H: at least 2 substituents on Ph ring
- o,o': C₁-C₄ alkyl, C₁-C₃ alkyl/Halo, CF₃, F, Cl, Et/OMe
- o,m: Cl, Oalkyl₂, CF₃
- o,m': F/Me, Me, Me/F, F/CF₃
- m,m': CF₃

monosubstituted derivatives:
- o: cPr, H, Et, OMe, OCF₃
- m: NO₂, NH₂, Aryl

trisubstituted derivatives:
- o,o',m: Et/ Et/F, Et/Et/F, Et/Et/Br, Et/F/F, F/F/Me, Et/F/Cl

NH mandatory

2-Imidazole < 4-Imidazole

In functional assay with h/r TAAR1
only H tolerated!

based on Kᵢ on h/rTAAR1 and hTAAR1

green < 0.5 μM
0.5 μM < orange > 5 μM
red > 5 μM
Profile of RO4992479
a Selective TAAR1 Full Agonist

- Good selectivity vs. other GPCRs
- Good physicochemical properties
- Low oral bioavailability in both mouse & rat

<table>
<thead>
<tr>
<th>TAAR1</th>
<th>human</th>
<th>mouse</th>
<th>rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>46 nM</td>
<td>51 nM</td>
<td>324 nM</td>
</tr>
<tr>
<td>Effic.</td>
<td>87%</td>
<td>74%</td>
<td>62%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>α2a</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>7.13 µM</th>
<th>Effic.</th>
<th>17%</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CEREP (panel of 60 targets)</th>
<th>clean</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>hERG IC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>&gt;10 µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>I&lt;sub&gt;1&lt;/sub&gt; IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Microsomal Stability

<table>
<thead>
<tr>
<th></th>
<th>human</th>
<th>mouse</th>
<th>rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl&lt;sub&gt;Mic&lt;/sub&gt;</td>
<td>13</td>
<td>59</td>
<td>--</td>
</tr>
<tr>
<td>MAB</td>
<td>68%</td>
<td>37%</td>
<td>--</td>
</tr>
<tr>
<td>Class</td>
<td>M</td>
<td>M</td>
<td>--</td>
</tr>
</tbody>
</table>

Phys.-chem. Properties

<table>
<thead>
<tr>
<th></th>
<th>logD</th>
<th>MW</th>
<th>Sol.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.62</td>
<td>214</td>
<td>410 µg/ml</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>pKa</th>
<th>PAMPA</th>
<th>3.42 x 10&lt;sup&gt;-6&lt;/sup&gt; cm/s</th>
</tr>
</thead>
</table>

SDPK

<table>
<thead>
<tr>
<th>i.v. dose</th>
<th>mouse</th>
<th>rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>64 ml/min/kg</td>
<td>66 ml/min/kg</td>
</tr>
<tr>
<td>Br./Pl.</td>
<td>2.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p.o. dose</th>
<th>mouse</th>
<th>rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>c&lt;sub&gt;max&lt;/sub&gt;</td>
<td>303 ng/ml</td>
<td>97 ng/ml</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>1.0 h</td>
<td>0.3 h</td>
</tr>
<tr>
<td>Bioavail. F</td>
<td>21%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Good selectivity vs. other GPCRs
Good physicochemical properties
Low oral bioavailability in both mouse & rat
Profile of RO4992479
a Selective TAAR1 Full Agonist

- Active in antagonizing cocaine-induced hyperlocomotor activity in mouse
- Anxiolytic-like effect in stress-induced hyperthermia (SIH) in mouse

![Chemical structure of RO4992479]

**Graph**

- **mTAAR1**
  - $K_i$ 28 nM
  - $EC_{50}$ 60 nM
  - 73% efficacy

- **Stress Induced Hyperthermia**
  - Effect on $\Delta T$
  - **No effect in TAAR1 KO mouse!!**
Synthesis of 2-Benzyl Imidazoles 

\( o,o' \)-disubstituted required an ad-hoc synthetic route

![Chemical structures and reaction schemes](image)

Benzylimidazolines and Benzylimidazoles  
**Structure Activity and Selectivity Relationship**

1) Restricted SAR  
No selectivity vs. α2  
Brain/Plasma <1

2) Restricted SAR  
Low selectivity vs. α2  
Often high clearance in PK  
Submicromolar inhibition of CYP (especially at 2C9)

3) Restricted SAR  
Low selectivity vs. α2  
Often high clearance in PK  
Submicromolar inhibition of CYP (especially at 2C9)

- All three series show a very restricted structure-selectivity-relationship
- Metabolite ID studies on RO4992479 showed extensive oxidation of o,o’-ethyl residues and GSH adduct formation

\[
\begin{array}{c|c|c}
R^1, R^2 & K_i \text{hTAAR1} & K_i \text{hTAAR1}/K_i \alpha_2 \\
\hline
\text{H} & 400 \text{ nM} & 4.7 \\
\text{o,o’-diMe} & 36 \text{ nM} & 4.5 \\
\text{o,o’-diEt} & 24 \text{ nM} & 100 \\
\text{o,o’-diPr} & 630 \text{ nM} & 14 \\
\end{array}
\]
Discovery of the 2-atom linker 4-Imidazole series

Successful Application of a SOSA Approach

Aminomethyl imidazoles are known adrenergic ligands – SOSA approach*

Selectivity for TAAR1 could be achieved by variation of substituents

4-Aminomethyl-Imidazoles

Structure Activity and Selectivity Relationship

<table>
<thead>
<tr>
<th>EC&lt;sub&gt;50&lt;/sub&gt; hTAAR1</th>
<th>R</th>
<th>Selectivity vs. α&lt;sub&gt;2a&lt;/sub&gt; (based on EC&lt;sub&gt;50&lt;/sub&gt; and IC&lt;sub&gt;50&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 nM</td>
<td>m-Cl</td>
<td>Good selectivity vs. α&lt;sub&gt;2&lt;/sub&gt;A</td>
</tr>
<tr>
<td>10 nM</td>
<td>H, m,m'-di-F</td>
<td></td>
</tr>
<tr>
<td>50 nM</td>
<td>m-Cl, p-F, m,p-di-F, p-NHC(O)Aryl, m-Me</td>
<td></td>
</tr>
<tr>
<td>100 nM</td>
<td>p-Cl, m-F, m-Cl-m'-F</td>
<td></td>
</tr>
<tr>
<td>300 nM</td>
<td>m-OMe, m-Cl, o'-F, p-F, m-Me, m-OCF&lt;sub&gt;2&lt;/sub&gt;CF&lt;sub&gt;2&lt;/sub&gt;H</td>
<td></td>
</tr>
<tr>
<td>Broader SAR allowed</td>
<td>m,p-di-Cl, m-Cl, p-F, m-[1-pyrrole]</td>
<td></td>
</tr>
</tbody>
</table>

Green > 200
200 > orange > 50
red < 50

Good PK possible
RO5073012 – a TAAR1 partial agonist

- Balanced TAAR1 efficacy profile across species
- Good selectivity vs. other GPCRs
- Good physicochemical properties
- Good oral PK profile in both mouse & rat

**Phys.-chem. Properties**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>logD</td>
<td>3.3</td>
</tr>
<tr>
<td>MW</td>
<td>250</td>
</tr>
<tr>
<td>Sol.</td>
<td>97 μg/ml</td>
</tr>
<tr>
<td>pKa</td>
<td>3.5 / 6.7</td>
</tr>
<tr>
<td>PAMPA</td>
<td>2.7 x 10^{-6} cm/s</td>
</tr>
</tbody>
</table>

**Microsomal Stability**

<table>
<thead>
<tr>
<th>Property</th>
<th>Human</th>
<th>Mouse</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl_{Mic}</td>
<td>18</td>
<td>18</td>
<td>70 μl/min/mg</td>
</tr>
<tr>
<td>MAB</td>
<td>46%</td>
<td>64%</td>
<td>30%</td>
</tr>
<tr>
<td>Class</td>
<td>M</td>
<td>M</td>
<td>H</td>
</tr>
</tbody>
</table>

**CEREP (panel of 60 targets)**

- clean

**α2a**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC_{50}</td>
<td>&gt; 50 μM</td>
</tr>
<tr>
<td>IC_{50}</td>
<td>= 11 μM</td>
</tr>
</tbody>
</table>

**hERG**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC_{50}</td>
<td>&gt;10 μM</td>
</tr>
<tr>
<td>IC_{20}</td>
<td>7.8 μM</td>
</tr>
</tbody>
</table>

**EC_{50}**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>23 nM</td>
</tr>
<tr>
<td>Mouse</td>
<td>33 nM</td>
</tr>
<tr>
<td>Rat</td>
<td>25 nM</td>
</tr>
</tbody>
</table>

**Effic.**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>35%</td>
</tr>
<tr>
<td>Mouse</td>
<td>25%</td>
</tr>
<tr>
<td>Rat</td>
<td>24%</td>
</tr>
</tbody>
</table>

**IC_{50}**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>25 nM</td>
</tr>
<tr>
<td>Mouse</td>
<td>33 nM</td>
</tr>
<tr>
<td>Rat</td>
<td>24 nM</td>
</tr>
</tbody>
</table>

**IC_{20}**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>24%</td>
</tr>
<tr>
<td>Mouse</td>
<td>25%</td>
</tr>
<tr>
<td>Rat</td>
<td>24%</td>
</tr>
</tbody>
</table>

**Microsomal Stability**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>18</td>
</tr>
<tr>
<td>Mouse</td>
<td>18</td>
</tr>
<tr>
<td>Rat</td>
<td>70 μl/min/mg</td>
</tr>
</tbody>
</table>

**MAB**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>46%</td>
</tr>
<tr>
<td>Mouse</td>
<td>64%</td>
</tr>
<tr>
<td>Rat</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Class**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>M</td>
</tr>
<tr>
<td>Mouse</td>
<td>M</td>
</tr>
<tr>
<td>Rat</td>
<td>H</td>
</tr>
</tbody>
</table>

**i.v. dose**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>Mouse</td>
<td>4.8 mg/kg</td>
</tr>
</tbody>
</table>

**CL**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>24 ml/min/kg</td>
</tr>
<tr>
<td>Mouse</td>
<td>40 ml/min/kg</td>
</tr>
</tbody>
</table>

**Br./Pl.**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>0.6</td>
</tr>
<tr>
<td>Mouse</td>
<td>6.6</td>
</tr>
</tbody>
</table>

**p.o. dose**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>Mouse</td>
<td>3.8 mg/kg</td>
</tr>
</tbody>
</table>

**c_{max}**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>1740 ng/ml</td>
</tr>
<tr>
<td>Mouse</td>
<td>519 ng/ml</td>
</tr>
</tbody>
</table>

**t_{1/2}**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>1.8 h</td>
</tr>
<tr>
<td>Mouse</td>
<td>1 h</td>
</tr>
</tbody>
</table>

**Bioavail. F**

<table>
<thead>
<tr>
<th>Species</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>86%</td>
</tr>
<tr>
<td>Mouse</td>
<td>67%</td>
</tr>
</tbody>
</table>

17
RO5073012 – a TAAR1 partial agonist
Active in key behavioural assays

Primary in vivo screening assay

Reversal of cocaine-induced hyperlocomotion in rats
→ indicative for schizophrenia

Reduction of immobility time in Forced Swim Test (FST) in rats
→ indicative for depression

RO5073012 – a TAAR1 partial agonist

- Balanced TAAR1 efficacy profile across species
- Good selectivity vs. other GPCRs
- Good physicochemical properties
- Some key safety flags need to be resolved!

**TAAR1**

<table>
<thead>
<tr>
<th></th>
<th>human</th>
<th>mouse</th>
<th>rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC50</td>
<td>23 nM</td>
<td>33 nM</td>
<td>25 nM</td>
</tr>
<tr>
<td>Effic.</td>
<td>35%</td>
<td>25%</td>
<td>24%</td>
</tr>
</tbody>
</table>

**α 2a**

EC50 > 50 μM

**CEREP** (panel of 60 targets)

Clean

**hERG**

IC50 > 10 μM

IC20 7.8 μM

**Microsomal Stability**

<table>
<thead>
<tr>
<th>ClMic</th>
<th>human</th>
<th>mouse</th>
<th>rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>18</td>
<td>70 μl/min/mg</td>
<td></td>
</tr>
</tbody>
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<table>
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<tr>
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<th>Sol.</th>
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<td>250</td>
<td>97 μg/ml</td>
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<table>
<thead>
<tr>
<th>pKa</th>
<th>PAMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 / 6.7</td>
<td>2.7 x 10^-6 cm/s</td>
</tr>
</tbody>
</table>

**CYP P450 Inhibition**

<table>
<thead>
<tr>
<th>IC50</th>
<th>3A4</th>
<th>2D6</th>
<th>2C9</th>
<th>1A2</th>
<th>2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4 μM</td>
<td>8.1 μM</td>
<td>1.0 μM</td>
<td>2.3 μM</td>
<td>1.3 μM</td>
<td></td>
</tr>
</tbody>
</table>

**GSH Adducts**

<table>
<thead>
<tr>
<th>human</th>
<th>rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLAG</td>
<td>FLAG</td>
</tr>
</tbody>
</table>

**In Vitro Tox**

<table>
<thead>
<tr>
<th>Ames</th>
<th>MNT</th>
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<tbody>
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<td>NEG</td>
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Reactive Metabolite Formation

Strong propensity to form GSH adducts

- Most selective imidazole compounds bear N-C linker (embedded aniline)
- Nearly all aniline-containing cmpds showed pronounced formation of GSH adducts upon metabolic activation in both rat and human liver microsomes

In line with mass peaks found:

- Aryl-NH₂ + GSH - 2H + O
- Aryl-NH-alkyl + GSH - 2H + O (M-alkyl) + GSH - 2H + O
Imidazole Series – conclusions at mid-LO stage

*In vivo-activity seen in several behavioral models*

**Attributes**
- **Selectivity** and **PK profile** suitable for use as POC compounds
- **Active in behavioural models** in rodents
- **Provided first insights** into behavioural pharmacology of TAAR1

**Liabilities**
- High DDI risk: **strong CYP inhibition** due to unsubstituted imidazole
- Only **N-C linker** affords sufficient selectivity
- N-C linker associated with **high reactive metabolite risk** (GSH adducts)
- Mainly partial agonists at TAAR1: full agonists rare
- Judged **unlikely to deliver a clinical candidate.** SERIES TERMINATED
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Preclinical Team - Sept 2007
Doing now what patients need next