

2004 Antiretrovirals Pipeline Report

11th Conference on Retroviruses and Opportunistic Infections
San Francisco, CA
8-11 February 2004
Prepared for
Treatment Action Group
By Rob Camp

Not so fast!

Where's my pipeline?

Pipelines are almost as delicate and fragile as the ecosystems they go trampling through. Oft times the way to get from the beginning to the end is not a straight line. Although that does remain the quickest way geometrically, there may be other factors at play. For oil to get to the Black Sea, sometimes the pipeline has to go around countries and political factions, rather than through them. And on the way, discoveries are made and decisions are taken.

Last year's pipeline report was warm and hopeful and excited. But over the course of the year, 2003 saw the "on-holding"-ing (dump it in the bucket) of SCH-C, the entry inhibitor that was moribund before the ink on the articles describing it was dry. According to Schering-Plough, it is on hold while SCH-D goes forward, and unless something more heinous than arrhythmia comes up with the D compound, C is not gonna be resuscitated. Roche gave us the end-of-year blues, dropping T-1249 due to "viscosity issues". It probably got a lot more viscous after the dramatically low sales numbers for T-20: by the end of the year 2003, they had 2500 people on drug worldwide. In order to dedicate more time and effort to selling T-20 (it wasn't getting ordered by itself—remember, 2 subcutaneous shots a day at \$20,000 a year), they couldn't devote anything more to T-1249. All integrase inhibitors (II) have been fossilized and won't be moving forward. The GSK/Shiniogi compound S-1360, greeted with much synergistic fanfare last year, was formally announced gonzo. GSK may have another II in the wings, but there is nothing to report on yet. MSD has been the leader in plotting the integrase gene and understanding its être. They report no news on either of their two L- compounds. Either they are restructuring their HIV division now that Dr Emilio Emini has left, or one of the reasons that Emini left is that there was nothing going forward. "We'll have to wait and see" is how I ended last year's report. We're still doing so. Of the seven drugs highlighted in TAG's pipeline report, July 2003, four are dead in the water.

In other disheartening news, Gilead sold back their Phase II NRTI DAPD to Emory University. With many difficult side effects ("lenticular opacities", kidney concerns) and not enough ingenuity regarding how to make a "salvage" drug work better, they gave up. Maybe a "real" Salvage company, as Boehringer Ingelheim now describe themselves, would be interested in picking up a Phase II NRTI?

I am putting the TMC- compounds and tipranavir back in the pipeline because otherwise, not much will be coming out of it in the near to middle future. See 2004 chart.

Extracellular agents

Attachment inhibitor: 043 (BMS)

Why Bristol needs to call their new attachment inhibitor by the same code as one of their pivotal registrational trials for atazanavir is beyond me. Be that as it may, it seems that their 806 "family" has produced its first offspring in 043. 043 is an oral agent and is inactive against HIV-2.

They described two Phase I studies, the first a single/double dosing study, with doses ranging from 200mg to 2400mg. The 400mg dose was repeated with ritonavir, and the 800 and 1800 mg doses were repeated with high fat food. Ritonavir increases exposure (AUC?) by 43%. The food doses showed a 3-5x increased exposure. The second study was a 14-day dose-ranging study from 400 to 1800mg BID with high fat (which is probably cheaper than ritonavir. They seem to be shying away from another drug that needs ritonavir). They report no SAEs, and in a private communication, Richard Colonna remarked on the "cleanliness" of the drug. 800mg BID looks like a reasonable dose, with increases of CD4s at +106/ μ l. Fatigue and diarrhea were among the grade 1/2 adverse events seen. No grade 3/4 events seen.

In another poster, resistance was clarified as gp120 mutations at V68A, M426L, M434I, S440R, M475R, as well as two mutations on the CD4 site, which means that it is overlapping in its binding pocket, W427V and S375W. It will be moving forward to Phase IB.

MAB/CCR5 inhibitors: PRO 542 + PRO 140 (Progenics)

No news from Progenics with 542, which blocks the CD4 receptor. PRO 140 saturates the CCR5 co-receptor. A SCID mouse model was presented at CROI where they showed concern that when the CCR5 co-receptor was blocked, a "switch" to CXCR4 occurs, which is a signal of more rapid HIV progression. They are continuing investigation, although leaving us with a concerned frown.

MAB entry inhibitor: TNX-355 (Tanox)

TNX-355 is a humanized IgG4 anti-CD4 domain 2 monoclonal antibody (MAB). It binds to the CD4 receptor, keeping HIV from entering the CD4 cell after binding. It is broadly inhibitory across all clades of HIV and inhibits both CCR5- and CXCR4-tropic virus.

The antibody attaches/"docks" alongside the CD4 receptor in a way that does not interfere with its regular function as a chemokine receptor. At this point, it blocks HIV from taking further steps in the process of entering the cell.

In a three-arm Phase Ib study, people were on a steady background regimen (unchanged), and the TNX infusion was added, either 10mg/kg once/week, 10 mg/kg induction, then 6mg/kg every two weeks, or 25 mg/kg every two weeks (this third, higher dose arm, was added when they saw that the first two doses were not nearing the maximum tolerated dose. They also note that they had "transient" reductions in viral load, which was probably the true driver for adding a higher dose third arm). They noted three SAEs. There were three people in the new high-dose arm, but they did not clarify if they were the three. Two of the SAEs were known to exist previously in the patients, depression and acute renal failure (due to renal insufficiency). The third, a seizure, may indicate a trend in receptor inhibitors. They did not report on the generation of natural antibody reactions.

A phase II study is planned, with optimized background therapy.

CCR5 co-receptor antagonist: SCH-D (Schering-Plough)

SCH-D is more bio-available than C, and has a half-life approaching 24 hours. It was looked at in a Phase I study at 10, 25 and 50mg BID. There was not much difference between the largest two doses in viral load reductions (1.56 vs 1.62 log 10) in this 14-day monotherapy study. Three serious adverse events were reported, one fever, one secondary syphilis, and one cerebrovascular accident that happened before dosing. The presenter then went on to say that in 275 dosings up to now, no grade 3/4 AEs have been seen, although there was some reported mild to moderate GI events. Lipids went up, cholesterol went down (no details, just sound bites). Receptor occupancy at two hours is between 93 and 99%. One person did change to X4 receptor, meaning that he may now fast track to AIDS (see related concern with Progenics' and Pfizer's molecules). The CD4 entry criteria was >200.

CCR5 co-receptor antagonist: UK-427,857 (Pfizer)

This oral Pfizer molecule is a CCR5 antagonist in phase I dose-ranging trials in humans. It works against isolates that utilize CCR5 for entry; however, it has no activity against CXCR4-tropic viral isolates. It is non-competitive with respect to chemokine binding. At CROI, they presented a poster on the X4 boy, the dual-tropic patient who was "mistakenly" entered into the trial, whose co-receptor usage went all to X4 (thus was "fast-tracked" progression-wise). His viral load was the only one of ten patients that did not go down—it remained the same. Looking closer, the investigators discovered that he was in fact, not R5-tropic (ie, he did not mainly use the CCR5 co-receptor at viral entry, but in fact was dual-tropic, he used both co-receptors). On cessation of study drug, his main tropism converted again, from X4 back to R5 and probably dual-tropism. This was a short 11-day trial, and it is not known if this reaction is more broadly significant for anyone who does switch to X4 while on treatment. It may point to the need for closer monitoring for the first two weeks or so while tropism is clarified in all patients.

CCR5 co-receptor antagonist: GW873140 (Glaxo)

Of course, GSK has a co-receptor antagonist as well. GW873140 was administered to 70 people in a single and multiple oral dose escalation study. Mild to moderate side effects included abdominal cramping, nausea and diarrhea. Food increased the AUC 1.7 fold and the C_{max} 2.2 fold. Co-receptor CCR5 occupancy by drug at 24 hours post-single dose was between 68 and 88%. Occupancy was >97% at 2 and 12 hour post-multiple-dosing measure points. Food increases the exposure by 1.7 fold. It has limited CNS penetration.

CCR5 co-receptor antagonist: AK-602 (Moravek)

602 binds to CCR5 at a different place, the extra-cellular loop-2 (ECL-2) than other antagonists (transmembrane domains), and may be interesting as a combination agent with other CCR5 blockers.

Co-receptor antagonists: AMD-887 + AMD-070 (Anormed)

887 is a CCR5 antagonist while 070 is an X4 antagonist. In some in vitro studies, they do not have cross-activity but in combination in fact completely inhibit viral replication in PBMCs. Is this a combination to keep an eye out for?

X4 co-receptor antagonist: KRH-2731 (Kureha)

KRH-2731 is an orally available X4 blocker, tested on mice, rats, and dogs. KRH is also an extracellular loop binder (like AK-602). At 10mg/kg it suppresses X4 in mice, and is 37% bioavailable in rats.

Integrase Inhibitors

V-165 (Rega Institute)

V-165 was reported on in an abstract that was actually focused on the complicated resistance mechanism of the integrase gene at the protein level.

The team at the Rega Institute for Medicine, Katholiek University, Leuven, Belgium, noted that the GSK and MSD integrase inhibitors were totally cross resistant, while V-165 still showed "activity" in vitro.

L-870,812, L-870,810 (MSD)

Does the L stand for Lost in action?

NRTIs

SN-1212/1461 (Koronis)

Koronis Pharmaceuticals' SN-1212 forces HIV's gene-replicating machinery to make so many mistakes that HIV ceases to be viable. Chemically it is considered a mutagenic deoxyribonucleoside. Lab tests have been unable to find or induce any HIV strains capable of resisting SN-1212's action. SN-1461 is the oral prodrug of SN-1212 and has been looked at in rats and dogs.

SPD-754 (Shire Biochem)

Shire did a PK study to look at its NRTI in a dose escalation monotherapy for 10 days. Due to what they call the "forgiveness" factor (higher intracellular concentrations), a BID dosing will move forward.

SPD-754 is less toxic than its racemic salt; in fact, the 8 monkeys who received the racemate (BC-10652) were put down/euthanized between weeks 13 and 15 due to a degenerative dermatopathy. The ones who received SPD-754 got hyperpigmentation (a deep blackening) on the palms of the hands, soles of the feet, lips, ears and/or tails, caused by an increase in melanosome population in melanocytes and other cells of the epidermis. In the oral presentation of SPD-754 + 3TC, it was observed that SPD-754 intracellularly was reduced some 6-fold when co-administered with 3TC. This antagonism would be the basis for not using these two agents together, and possibly only in the order of SPD-754 first, then 3TC (or presumably FTC) due to the sensitivity to the 184V.

Reverset (Pharmasset/Incyte)

Reverset is an NRTI with activity against HIV-1 and -2, an intracellular half-life of 17 hours, and no reported mitochondrial toxicity, with in vitro activity against AZT and 3TC resistant mutations. Pharmasset offered up a 10-day monotherapy dose escalation trial in naïve people >50 CD4s, at 50, 100, 200mg QD. Although 200mg showed the best PK data, CD4s increased the best with 100mg, and viral load at 100mg dropped by 1.80 log₁₀ (200mg not reported). Enteropathy (an intestinal disease) and bone marrow toxicity has been seen in rats. Hypopigmentation has been seen around the nose in female dogs. In humans, without grading, headache was seen in 33% of patients, fatigue in 17%, and the common cold (?) in 46% —the study took place in the fall. It cannot overcome resistances at codons D69 and Q151.

NNRTIs

GSK-678248 (Glaxo)

The active parent, 678248, is 25- to 400-fold more potent than its pro-drug, 695634. Interestingly, 678248 inhibited the primer unblocking reaction that contributes to AZT resistance (the D76N/K70R/T215Y/K219Q mutant). Moving forward into Phase IB.

TMC-125 (Tibotec)

A lovely resistance poster laid out the susceptibility codons of TMC-125. They seem to be at positions 101, 179, 181 and possibly 227 and 230, decreasing the efficacy of the drug. These four single mutations and one double mutation are worrisome (they cause a >10 fold change, although 4 may be the more realistic fold change to be concerned about. Looking at 4 fold, the 100, the 108 and 238 may be important, along with doubles at 181 + 188, 181 + 190, 179 + 181). A number of (at least 6) triple mutations are worrying. No efficacy data was presented; they have just started a number of trials after a 9-month hold due to rash issues that have now been "accepted" by the FDA.

Dupont follow-ups (BMS)

When BMS bought Dupont, they inherited a lot of NNRTIs. We thought they had forgotten about them. Fear not, tricyclic NNRTIs shall be back. In one poster, they lauded one (A-78277) that was killed at the last minute for cardiovascular "effects", but they did point out that this class has improved resistance profiles, significant improvements in activity, a potential increased genetic barrier and long half-lives. We'll stay tuned.

PIs

TMC-114/r (Tibotec)

Unfortunately, TMC-114 needs 100mg of RTV, usually BID, but otherwise may be considered an advance in PI therapy. Food also helps exposure (by some 40%). Response rates in this dose escalation study were similar, if not identical (by statistical analysis, not per person studied), for patients with >1 primary PI mutation, phenotypic resistance to all PIs, phenotypic resistance to lopinavir, and viral loads of more than 20,000. Baseline susceptibility to TMC was not predictive of these positive effects.

Maturation inhibitors

PA-457 (Panacos)

Panacos Pharmaceuticals' PA-457 is dubbed a "maturation inhibitor." It blocks a step late in HIV's replication cycle when new copies are packaged for export out of the cell. It is the first drug to act on this step in HIV's life-cycle. It is in its first safety trial now in non HIV-infected people. If that trial goes well, it will be given to about 60 HIV+ people this summer. PA-457 is a naturally-derived product: It is made from betulinic acid, which is found in the bark of birch and plane trees.

References

G Hanna, J Lalezari, et al, Antiviral Activity, Safety, and Tolerability of a Novel, Oral Small-molecule HIV-1 Attachment Inhibitor, BMS-488043, in HIV-1-infected Subjects, Abstr 141, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

P F Lin, H T Ho, et al, Characterization of a Small Molecule HIV-1 Attachment Inhibitor BMS-488043: Virology, Resistance and Mechanism of Action, Abstr 534, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

G Hanna, J-H Yan, et al, Safety, Tolerability, and Pharmacokinetics of a Novel, Small-Molecule HIV-1 Attachment Inhibitor, BMS-488043, after Single and Multiple Oral Doses in Healthy Subjects, Abstr 535, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

M Franti, L Ramos, et al, Control of HIV-1 Replication in the hu-PBL-SCID Mouse Model by an Anti-CCR5 Monoclonal Antibody, Abstr 537, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

J M Jacobson, D R Kuritzkes, et al, Phase 1b Study of the Anti-CD4 Monoclonal Antibody TNX-355 in HIV-1-infected Subjects: Safety and Antiretroviral Activity of Multiple Doses, Abstr 536, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

D Schurmann 1, R Rouzier 2, et al, SCH D: Antiviral Activity of a CCR5 Receptor Antagonist Abstr 140LB, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

M Westby, J Whitcomb, et al, Reversible Predominance of CXCR4 Utilising Variants in a Non-Responsive Dual Tropic Patient Receiving the CCR5 Antagonist UK-427,857, Abstr 538, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

J Demarest, K Adkison, et al, Single and Multiple Dose Escalation Study to Investigate the Safety, Pharmacokinetics, and Receptor Binding of GW873140, a Novel CCR5 Receptor Antagonist, in Healthy Subjects, Abstr 139, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

K Maeda, H Ogata, et al, Determination of Binding Sites of a Unique CCR5 Inhibitor AK602 on Human CCR5, Abstr 540, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

D Schols, K Vermeire, et al, In vitro Anti-HIV Activity Profile of AMD887, a Novel CCR5 Antagonist, in Combination with the CXCR4 Inhibitor AMD070, Abstr 539, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

T Murakami, A Yoshida, et al, KRH-2731: An Orally Bioavailable CXCR4 Antagonist Is a Potent Inhibitor of HIV-1 Infection, Abstr 541, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

M Witvrouw, V Fikkert, et al, Multiple Mutations in HIV-1 Integrase Confer Resistance to the Phase 1/2 Clinical Trial Drug S-1360, Abstr 632, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

K Harris, B Brabant, et al, SN1212/1461 a Novel Mutagenic Deoxyribonucleoside Analog with Activity against HIV, Abstr 532, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

R Bethell, J Adams, et al, Pharmacological Evaluation of a Dual Deoxycytidine Analogue Combination: 3TC and SPD754, Abstr 138, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

P Collins, L Shiveley, et al, Analysis of the Genotypes of Viruses Isolated from Patients after 10 Days Monotherapy with SPD754, Abstr 526, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

C Locas, S Ching, and S Damment, Safety Profile of SPD754 in Cynomolgus Monkeys Treated for 52 Weeks, Abstr 527, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

J Adams, J Sawyer, and L Shiveley, Intracellular SPD754 Triphosphate Pharmacokinetics following Administration of SPD754 Capsules, Abstr 599, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

R L Murphy, D Schürmann, et al, Tolerance and Potent Anti-HIV-1 Activity of Renset following 10 Days of Mono-therapy in Treatment-naïve Individuals, Abstr 137, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

G Roberts*, D Porter, et al, Kinetic and Thermodynamic Parameters for Binding of the Non-nucleoside Inhibitors GW678248 and GW695634 to Wild Type and 12 Mutants of HIV-1 Reverse Transcriptase, Abstr 529, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

J Vingerhoets, I De Baere, et al, Antiviral Activity of TMC125 against a Panel of Site-directed Mutants Encompassing Mutations Observed in vitro and in vivo, Abstr 621, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

S De Meyer, H Van Marck, et al, Phenotypic and Genotypic Profiling of TMC114, a Potent Next-generation PI, against Some 1600 Recent PI-resistant Clinical Isolates, Abstr 620, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.

M Peeters, B Van Baelen, et al, TMC114/RTV Activity in Multiple PI-experienced Patients: Correlation of Baseline Genotype, Phenotype, Pharmacokinetics, and IQ with Antiviral Activity at Day 14, Abstr 533, 11th Conference on Retroviruses and Opportunistic Infection. Feb 8-11, 2004. San Francisco CA USA.